

Patterns of concomitant allergic reactions in patients suggest cross-sensitization between octylisothiazolinone and methylisothiazolinone

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Summary

Background. Recent animal tests have indicated cross-reactivity between methylisothiazolinone (MI), octylisothiazolinone (OIT), and benzisothiazolinone (BIT).

Objectives. To retrospectively analyse concomitant reactions to different isothiazolinones in patients in an occupational dermatology clinic during the ongoing MI contact allergy epidemic.

Methods. We searched patch test files (January 2012 to February 2017) for patients with allergic reactions to OIT, BIT, and MI, and analysed their patch test results, occupations, exposure, and diagnoses.

Results. We found 61 (9.4%) allergic reactions to MI, 19 (2.9%) reactions to OIT and nine (1.4%) reactions to BIT in a total of 647 consecutively tested patients. Seventeen (89%) of the OIT-positive patients had concomitant reactions to MI, whereas only 3 (33%) BIT-positive patients had allergic reactions to MI. The MI reactions in OIT-positive patients were almost exclusively extreme reactions (+++). Exposure to OIT was identified in 26% of the OIT-positive patients, and 56% of the BIT-positive patients had been exposed to BIT.

Conclusions. Allergic reactions to OIT were strongly associated with extreme reactions to MI, which suggests cross-sensitization. However, BIT reactions were mostly independent.

Key words: benzisothiazolinone; CAS no. 2634-33-5; CAS no. 26530-20-1; CAS no. 2682-20-4; cross-reaction; methylisothiazolinone; nitrile glove; octylisothiazolinone; paints; patch test.

The epidemic of contact allergy to methylisothiazolinone (MI) (CAS no. 2682-20-4; Fig. 1) has raised interest in cross-sensitization among different isothiazolinones. A recent animal study using a modified lymph node

assay (1) showed cross-reactivity among MI, octylisothiazolinone (OIT) (CAS no. 26530-20-1; Fig. 1), and benzisothiazolinone (BIT) (CAS no. 2634-33-5; Fig. 1). In Belgium, MI-allergic patients more often had simultaneous allergic reactions to OIT than to BIT, and MI was considered to be the likely primary sensitizer in 40% of 15 OIT-positive patients (2). A large Information Network of Departments of Dermatology (IVDK) study concluded that simultaneous reactions in their patient population resulted from co-exposure to MI and BIT, and to MI and OIT, rather than from immunological cross-reactivity in patients primarily sensitized to MI (3). After finishing writing the manuscript, we found a new

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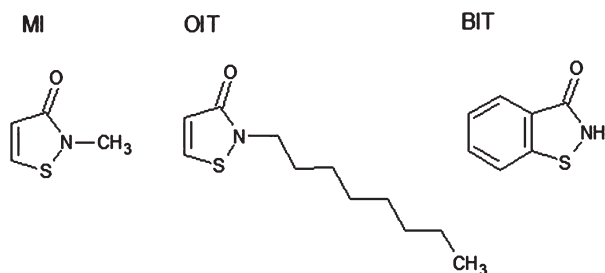


Fig. 1. Chemical structures of methylisothiazolinone (MI), octylisothiazolinone (OIT), and benzisothiazolinone (BIT).

report from Leeds that presents patch test results for OIT, BIT, MI and the mixture of methylchloroisothiazolinone (MCI) and MI (Kathon CG) in 1287 consecutively tested patients (4).

Finland has been severely affected by the MI contact allergy epidemic: in 2013, as many as 13.2% of patch tested patients had allergic reactions to MI in a Finnish multicentre study (5). At the Finnish Institute of Occupational Health (FIOH), we have found that allergic reactions to OIT have become common during the MI allergy epidemic, and we therefore wanted to analyse patterns of concomitant reactions to MI, OIT, and BIT, all three having been tested in almost every patient during the past decade. We chose the period from January 2012 to February 2017, as this probably covers the peak of the epidemic. We also present data on exposure to isothiazolinones in patients sensitized to OIT or BIT.

Materials and Methods

The FIOH has a clinic of occupational dermatology, and all of our patients have suspected occupational skin disease, and come from all parts of Finland. We ask them to bring samples of the suspected products from the workplace, and of the products they use at home.

We performed the patch tests with Finn Chambers® (Smart Practice, Phoenix, AZ, USA), in accordance with ESCD guidelines (6). We read the tests two or three times: on day (D) 2, D3 and D4, D2, D3 and D6, or D2 and D5, depending on the day of application (Monday, Tuesday, or Wednesday). We also asked the patients to inform us if they noticed any new reactions after the final reading.

We tested OIT (0.1% pet.; Chemotechnique Diagnostics, Vellinge, Sweden) and BIT (0.05% pet.; Chemotechnique Diagnostics) in the antimicrobial series throughout the study period. An in-house preparation of 0.03% MI aq. was included in our antimicrobial series until April 2015, whereas, in May 2015, we started testing MI

0.2% aq. (Chemotechnique Diagnostics) in our baseline series.

After patch testing, exposure to allergens yielding positive reactions is assessed collaboratively by a dermatologist and a chemist. This assessment often includes time-consuming enquiries to the manufacturers, and sometimes also chemical analyses if safety data sheets or product declarations do not provide sufficient information. Eventually, a decision is made on whether a contact allergy is of probable occupational origin. For a diagnosis of occupational allergic contact dermatitis (OACD), we need to identify sufficient exposure to the allergen, and the skin symptoms must be related to this exposure. Allergic reactions to work materials may also support the diagnosis of OACD.

We searched the patch test files for patients with allergic reactions to MI, OIT and BIT over the period from January 2012 to February 2017. We analysed the data on their occupations, patch test reactions, exposure, and diagnoses.

Results

During the study period, 647 consecutive patients were patch tested at the FIOH with OIT, BIT, and MI. OIT elicited allergic reactions in 19 (2.9%) patients, and BIT elicited allergic reactions in 9 (1.4%) patients (Table 1). MI was tested at a concentration of 0.03% in 428 patients and a concentration of 0.2% in 219 patients. MI elicited allergic reactions in 60 (9.3%) patients. The distribution was 21 extreme reactions (+++), 19 strong reactions (++), and 20 weak reactions (+). The frequencies of allergic reactions were 8.6% for the lower concentration and 10.5% for the higher concentration, but the lower concentration elicited more extreme reactions than the higher concentration (38% and 26%, respectively).

Sixteen of the patients had concomitant reactions to two of these isothiazolinones, and 2 patients reacted to all three isothiazolinones (Fig. 2). Seventeen (89%) of the OIT reactions occurred simultaneously with MI reactions, and, in 16 (84%) cases, the concurrent MI reactions were extreme (Table 1). Only three (33%) BIT reactions occurred with simultaneous reactions to MI (Table 1). Twenty-six per cent of the OIT-positive patients were exposed to OIT, and for BIT reactions the corresponding figure was 56% (i.e. exposure to BIT; Table 1). OIT elicited irritant reactions in 12 (1.9%) patients and doubtful reactions (?) in 7 (1.1%) patients (the sum of irritant or doubtful reactions was 19; 2.9%). BIT elicited irritant reactions in 10 (1.5%) patients and doubtful reactions in 9 (1.4%) patients.

Table 1. Patients with allergic reactions to octylisothiazolinone (OIT) and benzisothiazolinone (BIT); their occupations, their patch test reactions to OIT, BIT, methylisothiazolinone (MI), and methylchloroisothiazolinone (MCI)/MI, their isothiazolinone-related diagnoses, and their exposure to isothiazolinones

Patient	Occupation	OIT 0.1% pet.	MI 0.03% aq.	MI 0.2% aq.	MCI/MI 0.02% aq.	BIT 0.05% pet.	Isothiazolinone-related diagnosis, exposure and comments
1	Worker in production of heat elements	+		+++	++	–	OACD: MCI/MI in a biocide at work Previously MCI/MI and MI in hair waxes and detergents at home
2	Restaurant worker	+	+++		++	–	CA: past ACD caused by MCI/MI in a deodorant; MI in a dishwashing liquid
3	Cleaner	++	+++		+++	–	ACD: MI and MCI/MI in detergents at home
4	Bakery worker	+		+++	++	–	ACD: MCI/MI in a shampoo, a hair conditioner, a detergent, a shaving gel and a hand cleanser at home
5	Painter	+	+++		++	?+	OACD: MCI/MI, MI and OIT in several paints; MCI/MI in a sizing agent
6	Interior decoration shop assistant	++	+++		++	–	ACD on the face caused by MI in four leave-on cosmetic products; later OACD caused by MCI/MI, MI and OIT in tinting pastes and base paints
7	Construction worker	+	+++		+++	–	CA: MCI/MI in a shampoo and soap at home
8	Carpenter artisan	+	+++		++	–	OACD: MCI/MI in a glue, a hand cleanser and a screed; MI in four paints and a putty
9	Car mechanic	++		+++	+++	–	OACD: MI and MCI/MI in a hand cleanser at work; MCI/MI in a shampoo at home
10	Nurse	++	+++		++	–	CA: no isothiazolinones at work; MI in a dishwashing liquid at home
11	Assistant nurse	++	+++		+++	–	ACD: MI in a hair wax at home; MCI/MI in a shampoo and a wash cream at work
12	Singer	++		+++	+++	–	CA: MI in a dishwashing liquid did not explain the symptoms on the face
13	Carpenter	++		+++	++	?+	CA: present exposure not found; past exposure to isothiazolinones in construction work possible; also atopic dermatitis
14	Artisan	+++	+++		++	–	OACD: MCI/MI in acrylic and gouache colours
15	Dental nurse	+++		+++	+++	–	ACD: past exposure to MI or MCI/MI in a shampoo, a hair conditioner, detergents, a hand cleanser, a shower soap and a dishwashing agent at home
16	Agricultural holiday substitute	+++	–		IR	–	CA: OIT not found at work
17	Carpenter	+++	–		–	–	OACD: OIT in a paint
18	Painter	+++		+++	+++	+	OACD: MI, OIT, BIT and MCI/MI in paints and screeds
19	Tile setter	++	++		++	+	OACD: BIT and MI in waterproofing and bedding materials; OIT in an epoxy jointing paste
20	Pipe relining worker	–	–		+	+	CA: BIT not identified at work or home; MCI/MI in a shower soap; MI in a dishwashing liquid at home; wet wipes from work analysed: no isothiazolinones
21	Boilermaker/welder	–	–		++	+	CA: isothiazolinones not identified at work
22	Driller	?+	–		–	+	OCA: present exposure not found, but past exposure in metal-working fluids or their biocides probable
23	Construction painter	–	?+		++	++	OACD: BIT, MI and MCI/MI in paints, screeds, and a glue
24	Storeman	–		–	–	++	OACD: 20 ppm BIT found in Ansell Hylite nitrile gloves
25	Dental nurse	–		++	++	++	CA: MI in a dishwashing liquid at home; Nitrile gloves: no isothiazolinones found by chemical analysis
26	Paint factory worker	–		–	–	+++	OACD: Proxell GLX biocide: 17–25% BIT

ACD, allergic contact dermatitis; CA, contact allergy; IR, irritant reaction; OACD, occupational allergic contact dermatitis; OCA, occupational contact allergy.

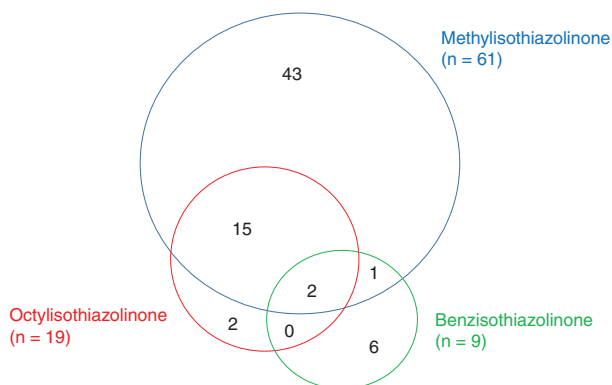


Fig. 2. Concomitant allergic patch test reactions to methylisothiazolinone, octylisothiazolinone, and benzisothiazolinone.

Discussion

The current epidemic of MI contact allergy is mainly caused by the use of MI as an independent preservative. MI was first introduced into industrial products in the early 2000s, and in 2005 it was approved in the EU for the preservation of cosmetics at a maximum concentration of 100 ppm.

In 2007, we presented a series of 8 patients with allergic reactions to OIT, covering the years 1991–2005, that is, mostly the pre-epidemic era (7). Certain or probable exposure to OIT was identified in half of the patients, and 2 of the patients had concomitant allergic reactions to 0.01% MCI/MI, but none had concomitant allergic reactions to BIT. We concluded that the simultaneous reactions were more probably attributable to separate exposure than to cross-sensitization. One of the MCI/MI-positive patients was, in fact, exposed to biocides that contained MI and OIT but not MCI/MI. The frequency of OIT reactions was 0.36% in 2222 patients tested with OIT, but, during this period, only approximately half of our total patient population were tested with OIT, so the frequency in our total patient population must have been lower.

Similarly, we presented a series of 20 patients with allergic reactions to BIT who were examined during the same period of 1991–2005 (8). Allergic reactions to 0.01% MCI/MI were observed in 4 (20%) of these patients, and reactions to OIT in 2 (10%). The low frequency of concomitant reactions did not support the notion of cross-sensitization between BIT, OIT, and MCI/MI.

In the present series, the situation is completely different as regards allergic reactions to OIT: first, they have become more frequent, involving 2.9% of our patient population; and second, a great majority now appear

in combination with extreme allergic reactions to MI. Although the frequencies in our present and former study are not directly comparable, a 10-fold difference between the two studies, or perhaps even more, can be estimated. In the present study population, we identified exposure to OIT in a lower percentage of the OIT-allergic patients than in our former study (7). In almost half of the cases, OIT reactions were better explained by cross-sensitization to MI and/or MCI than by specific exposure to OIT. This is in perfect accordance with the above-mentioned Belgian study (2). The Belgian group has noted that a commonly used patch test concentration of OIT of 0.025% pet. may possibly not be high enough to detect cross-reactivity with MI (9). At the FIOH, since 1991, we have always used a higher concentration of 0.1% OIT. In the IVDK study, only 50% of OIT-positive patients had concomitant reactions to MI (3). The IVDK study differs in several respects from the present study: it used a lower OIT concentration of 0.025%, and OIT and BIT were used only in targeted testing, MI was systematically tested in only a small proportion of patients, and the MI test concentration was 0.05% aq. There might also be a difference in exposure to MI in the populations of the countries contributing to the IVDK and of Finland. According to our experience, OIT 0.1% pet. is irritant in some patients, and false-positive reactions are possible. However, the majority of OIT reactions in the present series were clearly strong or extreme reactions, and all but one were connected with either exposure to OIT or strong/extreme reactions to MI. Typically, false-positive reactions are weak and occur at random. We share the opinion of the Belgian group that OIT should be tested at a concentration higher than 0.025% (9).

The drastic increase in the frequency of allergic reactions to OIT probably derives partly from primary sensitization to MI, but it is also possible that exposure to OIT has increased since the 1990s and early 2000s: in relation to the total number of patients tested, we have now found relevant allergy to OIT, that is, combined contact allergy and exposure to OIT, at a frequency of 0.8%, whereas in our former study the corresponding percentage was 0.1% (4 of 3904). This multi-fold difference cannot be wholly explained by targeted OIT testing in the former study.

As regards BIT, the present results did not essentially differ from the results of the IVDK study or the Belgian study (2). None of the studies suggest cross-sensitization between MI and BIT, and concomitant exposure remains the probable explanation for simultaneous reactions. This might be attributable to structural differences, BIT being an aromatic compound, and MI and OIT being aliphatic compounds. The test concentration of BIT, 0.05%, is relatively low in comparison with 0.1% for OIT and 0.2% for MI. It is possible that a higher

concentration would detect more simultaneous allergic reactions in MI-sensitized patients. Higher concentrations, for example up to 0.2%, of BIT, and also OIT, could be studied to determine the true frequency of concomitant allergic reactions in MI-positive patients. However, the irritant potential of the chemicals already discussed might limit the increase in test concentration.

The above-mentioned current English study presents results that are quite similar to ours: 75% of OIT-positive patients had concurrent allergic reactions to MI, and only 10% of BIT-sensitized patients reacted to MI (4).

It is possible that the frequency of BIT reactions has also increased to some extent (0.5% in the former study and 1.4% in the present study in relation to the total number of patch tested patients), but, as the first study involved targeted testing, the figures are not directly comparable.

As regards the OIT-containing and BIT-containing products in the present study, the majority of our sensitized patients had used paints, paint ingredients, and other products used in painting, such as screeds. A

decade ago, we had a small epidemic of BIT contact allergy resulting from the use of disposable vinyl gloves (8). The present study population includes a storeman with hand dermatitis who was sensitized to BIT and had used thick nitrile gloves that were shown to contain some BIT by chemical analysis. We have previously analysed BIT in several types of rubber gloves, but this is the first time that this finding has coincided with contact allergy to BIT in a patient.

As we now test all of our patients with OIT and BIT, we do not advise our MI-positive patients to avoid OIT or BIT if they have negative test results with these. In centres in which OIT and BIT are not routinely tested, it can be wise to have a different policy: at least patients with extreme reactions to MI should be warned about cross-allergy to OIT.

In conclusion, allergic reactions to OIT were common, and mostly concurrent with extreme reactions to MI, which suggests immunological cross-reactivity between the two chemicals.

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