

Repeated open application test with methylisothiazolinone in individuals sensitive to methylchloroisothiazolinone/methylisothiazolinone

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Methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) are chemically closely related. Patients who are hypersensitive to MCI/MI do not react positively to the MI concentration present in the baseline test solution of MCI/MI 100 ppm (1). When MI was introduced as a preservative in cosmetics in 2005, we lacked knowledge on whether elicitation of dermatitis would occur in patients hypersensitive to MCI/MI when they used a leave-on product preserved with MI. We also lacked knowledge on whether a patient allergic to MI at patch testing would react when exposed to MI at 100 ppm in leave-on products. Therefore, within the European Environmental and Contact Dermatitis Research Group (EECDRG), the Malmö clinic initiated a repeated open application test (ROAT) study to investigate individual clinical relevance in patients testing positively with MCI/MI 100 ppm and/or with MI at any of the three concentrations tested, that is, 1000, 1500 or 2000 ppm MI (2).

Five dermatology departments within the EECDRG participated. All had tested MCI/MI and MI separately in their baseline series, and when a dermatitis patient reacted to either MCI/MI 100 ppm or to any of the three concentrations of MI, they were asked whether they would perform a ROAT. Fifteen patients with contact allergy to 100 ppm MCI/MI and/or MI participated (Table 1). The test period was 1 October 2005 to 30 June 2006. The exclusion criterion was contact allergy to parabens.

The ROAT was performed with two sets of creams for each patient. The Hospital Pharmacy at Skåne University

Hospital, Malmö, Sweden manufactured the creams after receiving instructions from the Malmö department. The base cream was Aqueous cream ATL-K, a basic, bland moisturizer with no fragrance (Apoteksbolaget AB, Solna, Sweden). One set of cream contained the preservatives methylparaben 0.1% and propylparaben 0.2%, and the other set of cream contained MI at 100 ppm from Neolone™ 950 (at the time, Rohm and Haas Company, Philadelphia, PA, USA). Creams were dispersed into 15-g tubes numbered by the Malmö department. The tubes were also marked with red tape for treatment of the left arm and blue tape for treatment of the right arm, and sent from Malmö to the participating clinics. A set of two creams, one containing the parabens and the other MI, was thus given to each patient. The creams were randomly allocated to the arms. Patients were instructed to apply the creams twice daily for 2 weeks to the outer aspect of the upper arm on an area of 5 × 5 cm. The amount of cream to be used at each application corresponded to ~50% of the area of the fifth fingernail, that is, ~3 mg/cm². Inspection of the upper arms was performed by a dermatologist immediately prior to the ROAT and after 1 and 2 weeks, when the study terminated. The minimal requirement for a positive reaction was erythema and infiltration covering at least 25% of the area that was treated with the respective cream. If an area was positive after 1 week, application to that area was stopped. In this article, a positive ROAT result is equivalent to dermatitis on skin exposed to MI.

McNemar's test, one-sided, was used to compare the ROAT outcome between the MI-treated area and the paraben-treated area. A *p*-value of < 0.05 was considered to be statistically significant.

Of the 15 patients, 9 reacted to MCI/MI 100 ppm, and 9 to MI; thus, 3 reacted to both MCI/MI and MI. Eight had a positive ROAT result on the area treated

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Table 1. The outcome of repeated open application tests with methylisothiazolinone-containing cream in 15 patients hypersensitive to methylchloroisothiazolinone/methylisothiazolinone

Clinic	Patient no.	Outcome of ROAT with MI-containing cream	No. of applications	Reactivity to MCI/MI (ppm) 100	Reactivity to MI (ppm)		
					1000	1500	2000
Malmö	1	Negative	28	++	—	—	—
	2	Positive	15	+++	—	++	+++
	3	Positive	23	+++	—	—	—
	4	Positive	29	+	—	—	NT
	5	Positive	29	+	+	+	NT
	6	Negative	28	—	+	NT	NT
	7	Negative	28	+	—	NT	NT
	8	Positive	15	+	—	—	NT
Strasbourg	1	Positive	14	—	—	—	+
Coimbra	1	Positive	21	—	++	—	NT
	2	Negative	27	—	+	++	NT
	3	Negative	26	—	++	—	NT
Leuven	1	Positive	14	++	+	NT	NT
	2	Negative	28	—	—	—	+
	3	Negative	24	+	—	—	—
Total	15	8	—	9	6	3	3

NT, not tested.

with the MI-containing cream ($p = 0.004$). Of 9 MI-allergic patients 5 had a positive ROAT result and 4 had a negative ROAT result ($p = 0.031$). Of 9 MCI/MI-allergic patients, 6 had a positive ROAT result and 3 had a negative ROAT result ($p = 0.016$). Two patients only reacted to MI and were also ROAT-positive. Three patients were only allergic to MCI/MI and were also ROAT-positive.

Discussion

ROATs can be used scientifically to investigate whether a contact allergy is clinically relevant if the exposure is such as one would expect in real life. However, control patients, not allergic to the allergen under investigation, must then be used, and a statistically significant difference in the outcome of the ROAT is needed. In the everyday clinic, we may use ROATs to determine whether a patient who is allergic to an allergen at patch testing will react to a product containing the allergen in question, even if we cannot state that the dermatitis is an allergic contact dermatitis. It shows that the patient develops dermatitis from the product and should avoid it. However, in our daily practice, we use ROATs in selected cases to investigate the clinical relevance of a contact allergy.

Recently, a single-blind ROAT study was conducted in Finland, in which 33 patients who were hypersensitive to MI were instructed to apply twice daily a lotion preserved with 100 ppm MI to one antecubital fossa for 2 weeks, and

another lotion not containing MI to the other antecubital fossa (3). Ten had a positive reaction on the MI-treated areas (30%). Our study presented here was also performed to mimic real-life exposure to MI in cosmetics. We did not have any control patients, but had one bland cream not containing MI to enable the patient and the dermatologist performing the readings to be blinded to the exposure. We have thus shown that a patient who reacts positively to MCI/MI 100 ppm at patch testing will develop dermatitis if he or she is exposed to a cream containing MI at 100 ppm ($p = 0.016$). The explanation for this is probably cross-reactivity between MCI/MI and MI (4). This means that we will tell those of our patients who are sensitized to MCI/MI to avoid contact with MI-preserved products, at least with those preserved with high concentrations such as 100 ppm. From our study, it is also obvious that an individual who is allergic to MI should avoid products containing this preservative. In a Danish ROAT study from 2011, 18% of MI-allergic patients reacted to a concentration of MI in a liquid preparation that was 20 times lower than 100 ppm, but the authors state that 'the results cannot be directly compared with exposures from cosmetics or other products, because the vehicle may influence the reactivity in already sensitized individuals' (5).

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