

Isopropyl myristate recommended for aimed rather than routine patch testing

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Isopropyl myristate (IPM) is considered a very weak sensitizer. Patch test results with 20% IPM in petrolatum (pet.) in 8117 patients and 10% IPM in pet. in 4554 patients between January 1992 and December 2001 by the IVDK are presented. While irritant and questionable reactions were frequently observed, especially with 20% test concentration and 2-day patch test exposure, respectively, and a decrescendo pattern was common, morphologically positive reactions at day 3 were seen in only 16 patients, i.e. altogether 0.13%. In line with previous clinical and experimental evidence, our results indicate that IPM is an extremely weak sensitizer or possibly, in our material, not a sensitizer at all. IPM should thus not be tested routinely, but only in the case of suspected exposure as a possible source of allergic contact dermatitis, e.g. to cosmetics and perfumes, to avoid an unacceptable reduction of the positive predictive value of the test.

Key words: CAS 110-27-0; contact allergy; cosmetics; isopropyl myristate; patch testing.

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In a review on appropriate patch test concentrations of cosmetic ingredients, isopropyl myristate (IPM, tetradecanoic acid 1-methyl ester, CAS 110-27-0) has been mentioned as being present in 2246 of 19 000 cosmetic formulations on file at the US Food and Drug Administration (FDA) in 1980 (1). The authors recommended 5% petrolatum (pet.) for patch testing with IPM. To the best of our knowledge, up to that time, only a few cases of contact allergy to IPM had been published:

- (1) a 19-year old woman sensitized after 6 months' use of a feminine hygiene spray (2),
- (2) 6 patients with allergic contact dermatitis from an antibiotic-steroid spray, reacting positively on patch testing with the spray and IPM (as is; 12 controls negative) (3).

As appropriate test concentrations, 2%, 5% and 20% in pet. and 10% in alcohol have been recommended (4).

Patients and Methods

Starting in the late 80s, the German Contact Dermatitis Research Group (DKG) and the Information Network of Departments of Dermatology (IVDK) network (<http://www.ivdk.org>) included

IPM (20% pet., provided by Hermal, Reinbek, FRG) in the 'topicals' test series. After a first analysis of 1990/1991 IVDK data on 2054 patients did not reveal a single positive reaction, similarly to previous results of Fregert and Hjorth (5), but only 10 questionable and 3 irritant reactions (6), IPM was eliminated from the DKG test series by June 1994. Later on, 8 centres continued to patch test with IPM 10% pet. Patch test results obtained between January 1992 and December 2001 by the IVDK partners are presented.

Results

Until the end of 1994, 7675 patients were patch tested with IPM 20% pet. (29.8% of all patients tested during that period) and another 442 patients thereafter. Conversely, already during 1994, 271 patients were tested with IPM 10% pet. Since January 1995, 4283 more patients were patch tested with IPM 10% pet. in 8 centres of the IVDK. A summary of results is presented in Table 1. Analysis of the reaction pattern revealed frequent decrescendo reactions (from day 1 or day 2 to day 3):

Table 1. Patch test results with isopropyl myristate (IPM) in petrolatum (1992-2001)

Concentration	N-test	?	IR	+	++/+++	% positive (95% CI)	RI	PR
20%	8117	43 ^a	5 ^b	6	2	0.099 (0.043-0.19)	-0.71	75%
10%	4554	9 ^c	2 ^c	7	1	0.18 (0.076-0.35)	-0.16	88%

RI = reaction index (18); PR = positivity ratio (% weak positive reactions among all positive reactions); IR = irritant reaction; ? = doubtful reaction.

^a42 of these with 2 D allergen exposure (used in 60.2% of patients).

^bAll 5 with 2 D allergen exposure (used in 60.2% of patients).

^cAll 9 and 2, respectively, with 2 D allergen exposure (used in 93.7% of patients).

- (1) for 10% test concentration, 7 patients with ? (doubtful) to negative, 6 with + to negative and 7 with + to ? reactions,
- (2) for 20% test concentration, 41 patients with ? to negative, 6 with + to negative and 1 with + to ? reactions.

Almost all patients tested with IPM were also tested with lanolin alcohol (12 285 of 12 671), which caused 4.6% positive (+ to +++) reactions in this group, compared to 3.9% in the total group of 83 802 patients tested (1992-2001). Agreement between positive IPM and lanolin patch test reactions did not exceed chance (Cohen's kappa: 0.001, 95% CI: -0.005-0.007): 13 patients were positive to IPM alone, 568 to lanolin alcohol alone and only 1 to both allergens, the remainder concordantly negative.

In 5 of 16 patients with + or ++ reactions to IPM (current), and in 1 case (previous), relevance has been postulated (e.g. because of previous intolerance of different topicals), but not definitively proven. Routine anamnestic data of these 16 patients were largely unremarkable, including a median age of 42 (range: 22-88) and a proportion of 56% females. The MOAHLFA index for IPM-positive versus IPM-negative patients did not show statistically significant differences ($P > 0.05$, Fisher's exact test - M: 44% versus 35%, O: 6% versus 10%, A: 25% versus 18%, H: 38% versus 26%, L: 6% versus 11%, F: 6% versus 17%, Age 40+: 50% versus 62%).

Comment

IPM still is widely used in cosmetics [e.g. in fragrances, where the maximum concentration is 2%, amounting to 100 000 lb/year in the US (7)] and topical medicaments [e.g. in 119 different topical drug formulations on the German market, according to 'Rote Liste 2002' (8)]. Despite extensive exposure to IPM, we could not find evidence that IPM is a frequent allergen. This finding is in line with results of several human maximization tests or repetitive insult patch or use tests in healthy volunteers, which have produced no evidence of a noteworthy sensitizing potential (9). Rather, IPM may be mildly irritant under occlu-

sive application, in particular if tested at 20% pet., in view of predominantly questionable or irritant reactions and the frequent occurrence of decrescendo reactions.

This view is supported by experimental data to a certain extent: based on their results with a repetitive, occlusive irritation model, utilizing rabbits and humans. Campbell and Bruce (10) concluded that their 'studies support the use of IPM as a model species-variable skin irritant...'. Although irritation in humans was much less than in rabbits, in accordance with previous animal/human studies reviewed in this article (10), and the volunteers had been exposed to pure IPM for 1-4 successive days, it is obvious that IPM is not entirely non-irritant. The observation that in our patients irritant or questionable patch test reactions with either concentration almost exclusively occurred with 2-day patch test application, whereas 'positive' reactions were more or less evenly distributed among patients exposed for 1 versus 2 days (data not shown) may further support this notion. Concerning skin sensitization, experimental data have produced no evidence of IPM being a sensitizer (9, 11); weakly positive results obtained in a local lymph node assay have been considered false-positive by the authors (12).

The combination of the 2 factors - a rare allergen and a marginal irritant at the same time - may raise concerns about the interpretation of + reactions, i.e. whether these are always truly allergic or whether they are false-positive, because the positive predictive value of a 'positive test' will be quite low in this situation. Clinical studies of various sizes reporting patch test results with IPM found no positive reactions (5, 6, 13, 14) in patients tested consecutively or in a more aimed manner. Conversely, a few positive reactions were observed in 2 series, e.g. in patients tested for suspected cosmetic allergy [1.2% (15), using 10% IPM in ethanol] or in 2 of 133 and 1 of 124 patients, respectively, with no history indicative of exposure to IPM-containing products tested with IPM 100% and IMP 50% pet., respectively (16). Interestingly, 11 of 51 lanolin alcohol-allergic

patients had positive reactions to IPM (10% in ethanol) in another previous study (17). However, we did not find any evidence of cross-reactivity in our data, which is in good accordance with theoretical considerations.

In conclusion, we (i) would recommend performing a repeated open application test (ROAT) or use-related test in case of a presumably positive test reaction and (ii) would be reluctant to test IPM routinely, i.e. without apparent exposure, supported from the patient's history. As yet, there is no well-established concentration and vehicle for such a ROAT ($\times 2$ daily for 7 days). For practical reasons, the patch test preparation (e.g. 10% pet.) could be used. This suggestion is supported by the observation that higher concentrations or the combination of IPM with other vehicles intrinsically more irritating than pet. are capable of producing mild irritation after prolonged (21-day) repeated open application $\times 1$ daily (9).

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