

Late-appearing patch test reactions to carvone do not need to be signs of active sensitization

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A controlled and randomized use test with L-carvone in a toothpaste on individuals with or without contact allergy to carvone was performed.¹ One week before the use test, a patch test with L-carvone was performed in 37 volunteers. In two volunteers with a negative carvone test 1 week before the use test, late-appearing reactions were documented 3 weeks after the patch test.¹ After the termination of the use test, a retest with L-carvone was performed in these two volunteers with late-appearing reactions to carvone. Positive tests to carvone were documented already on reading day (D) 3 in both volunteers. In this paper, we explain why late-appearing patch test reactions to carvone followed by a positive retest within 3 days, do not need to be equivalent with active sensitization.

CASE REPORTS

Two females, 77 and 72 years old, with oral lichenoid reactions participated in the controlled and randomized use test with toothpastes with or without carvone in individuals with or without contact allergy to carvone.¹ A patch test with carvone in acetone in 10 serial dilutions from 5.0% w/v down to 0.00158% w/v was performed 1 week prior to the start of the use test.¹ At the same time three toothpastes in water at 50.0 w/v and 5.0% w/v% were patch tested. One of the toothpastes contained 1.0% w/w L-carvone. Fifteen microliters (30 $\mu\text{L}/\text{cm}^2$) of the test preparations² were applied in Finn chambers[®] (8 mm Ø, SmartPractice, Phoenix, AZ, USA) mounted on Scanpore[™] tape (Norgeplaster A/S, Vennesla, Norway) and placed on the subjects' upper back. The placement of the different preparations was randomized. The test readers were unaware about the placement of the individual preparations. Occlusion time was 48 h which was followed by test readings on D3 and D7. Reactions were classified according to the guidelines of the International Contact Dermatitis Research Group.³ No communication was allowed between the tested individuals and the reading dermatologist. The dermatologist did not know whether the tested individual suffered from oral lichenoid reactions and had carvone allergy or not.

No reactions were noted to any of the carvone dilutions, neither to the toothpastes.

After 20 and 21 days, the two females noted itching erythematous reactions on the back which were verified by a dermatologist, still without information on disease, carvone allergy, and placement of the test preparations.

After the termination of the use test, it was found that the late-appearing reactions were directed toward carvone and the carvone-containing toothpastes in both females, who had been randomized to use the toothpaste with 1% carvone (Table 1).

A retest with L-carvone in petrolatum at 5% w/w was performed with positive (allergic) reactions in both females on D3 (Table 1).

DISCUSSION

In a paper on late-appearing patch test reactions to para-phenylene diamine (PPD) followed by a retest with PPD,⁴ the following conclusion was drawn: "In our study 7 patients were re-tested with PPD, 5 (71%) reacted within 3 days, proving active sensitization." Following this statement, the two females would have been actively sensitized when patch tested to carvone 1 week prior to the use test.¹ However, both females were recruited to the study because of a previous diagnosis of oral lichenoid reactions and carvone allergy with a+ and a+++ reactions, respectively, when patch tested with our dental series containing carvone 5% in petrolatum 13 and 18 years earlier, respectively. Thus, the patients were not actively sensitized. It has been pointed out, in a paper on late reactions, that active sensitization is only one possible explanation for late reactions.⁵ The same pattern with late-appearing patch test reactions not being indications of active sensitization due to the patch test procedure has been reported earlier in patient cases⁶⁻⁸ but also in experimental patch test studies with gold⁹ and acrylates.¹⁰

TABLE 1 Patch test reactions to carvone and toothpastes in two females with late-appearing reactions after the first patch test occasion.

Test occasion	Test preparation in %	Test reaction	
		Female 77	Female 72
First—1 week prior to use test, readings D3 ^a and D7	Carvone ^b 5–0.000158	–	–
	Toothpaste ^c A 50 + 5	–	–
	Toothpaste B 50 + 5	–	–
	Toothpaste C 50 + 5	–	–
First—1 week prior to use test, reading D20 ^d and D21 ^e	Carvone 5	++	++
	Carvone 1.58	++	+
	Carvone 0.5	++	+
	Carvone 0.158	+	+
	Carvone 0.05	–	+
	Carvone 0.0158–0.000158	–	–
	Toothpaste A ^f 50	++	+
	Toothpaste A 5	–	–
	Toothpaste B 50 and 5	–	–
	Toothpaste C 50 and 5	–	–
Second—after termination of use test, reading D3	Carvone ^g 5	+	+

^aDay 3.^bCarvone in acetone w/v.^cToothpaste in water w/v.^dFemale 77.^eFemale 72.^fToothpaste A contained 1% carvone.^gCarvone in petrolatum w/w.

It is of utmost importance not to automatically accept late-appearing patch test reactions beyond D10 followed by a positive retest on D3–D7 as a proof of active sensitization. Indeed, active sensitization might be the explanation to this pattern, but the retest should always include dilutions of the putative sensitizer. Positive retest reactions to 100 times lower concentrations (doses/cm²) than the concentration which initially was negative 1 week prior to the use test, strongly support active sensitization.^{11–13}

Lowering the patch test concentration/dose based on incomplete investigations on possible active sensitization due to the patch test procedure should be avoided as this will have a negative impact on diagnostics and prevention of non-occupational and occupational allergic contact dermatitis.

AUTHOR CONTRIBUTIONS

Magnus Bruze: Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; data curation; resources. **Camilla Ahlgren:** Conceptualization; investigation; methodology; validation; visualization; writing – review and editing; data curation; resources. **Marléne Isaksson:** Conceptualization; investigation; methodology; validation; visualization; writing – review and editing; data curation; resources. **Liv Kroona:** Conceptualization; investigation; funding acquisition; methodology; validation; visualization; writing – review and editing; project administration; data curation; resources.

CONFLICT OF INTEREST STATEMENT

Magnus Bruze is a member of the expert panel for fragrance safety, <http://fragrancesafetypanel.org/>. Marlène Isaksson has worked as consultant for IFRA, International Fragrance Association.

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Long-lasting allergic contact dermatitis and positive patch test reactions to doxepin

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Doxepin is a tricyclic antidepressant drug with potent H1- and H2-antihistaminic properties. Its chemical structure is similar to that of phenothiazines, which are known contact sensitizers. Topical doxepin, used to relieve pruritus, is a well-known inducer of allergic contact and photocontact dermatitis. Here, we present a patient with doxepin-induced allergic contact dermatitis (ACD) showing unique clinical and patch test findings.

CASE REPORT

A 51-year-old non-atopic Turkish woman presented with pruritic eczema at the application site of topical doxepin hydrochloride 5% cream (Assos Pharmaceuticals, İstanbul, Turkey) on the right shoulder and arm (Figure 1A,B). The lesions developed on the third day of the application, but the patient did not remember that she had used doxepin in the past. Doxepin cream was stopped, and the eczema faded slightly with topical corticosteroids within 10 days. The patient changed her possibly doxepin-contaminated clothes and avoided doxepin and cross-reacting drugs. However, the lesions showed episodic flare-ups in the following 2 months,

fading slowly with topical corticosteroids. Systemic corticosteroids were used for 3 weeks, and the lesions disappeared completely.

Six months later, patch testing according to the European Society of Contact Dermatitis (ESCD) patch test guideline¹ showed strong/extreme positive reactions to doxepin 5% cream 'as is' (Figure 1C,D) and to a dilution series of doxepin hydrochloride tablet down to 0.01% in petrolatum (pet.) and aqua (aq.) (Table 1; Figure 1E-G). We did not perform patch testing with doxepin in healthy controls, and we considered the patch test reactions positive only when they showed crescendo- or plateau-positive patterns in the dilution series on at least 2 consecutive days. The repeated open application test (ROAT) with doxepin cream became positive on Day 3 after 5–6 applications (Table 2), according to the modified reading scale of the ROAT as described in the ESCD patch test guideline.¹

Six weeks after patch testing, the patient presented with a pruritic papulovesicular reaction on sites of the positive patch test reactions to doxepin hydrochloride tablet 0.01 pet. and 0.01% aq. (Figure 2A-C). She denied any further exposure to doxepin. Histopathology showed epidermal spongiosis and dermal perivascular mononuclear cells, consistent with a long-lasting positive allergic patch test reaction. Intraleisional injection of 0.2 mL triamcinolone acetonide (40 mg/mL) on one