CLINICAL REPORT

Carvone Contact Allergy in Southern Sweden: A 21-year Retrospective Study

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Carvone (l-carvone), a mint flavour in spearmint oil, is considered a mild skin sensitizer. Carvone-sensitization may be linked to oral/perioral signs and oral lichen planus, but studies are sparse. The prevalence of patch test reactions to carvone and relevant findings from the positive group were investigated. Records for patch-tested patients at the Malmö clinic, for the period 1996 to 2016, were studied. Carvone-positive and carvone-negative patients were compared regarding patch test data from baseline series and dental series. Dental series-tested carvone-positive patients were also compared with a matched group. A total of 147 out of 4,221 referred patients had a positive patch test to carvone. Sensitized patients had higher mean age and were primarily women; 73% had oral signs and 57% had oral lichen. Concomitant patch test reactions to gold, nickel and mercury were common. In the matched group-comparison carvone-positive patients had a higher frequency of oral lichen, but no difference was found in sensitization to gold and mercury.

Key words: l-carvone CAS; 6485-40-1; spearmint; patch test; allergens; contact allergy; oral lichen planus; oral lichenoid lesions.

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SIGNIFICANCE

Carvone is a mint flavour found in most oral healthcare products. This study investigates the prevalence of contact allergy to carvone and describes common features of affected patients. In a cohort of 4,221 tested patients 3.5% had contact allergy to carvone. These patients often had oral signs and variants of oral lichenoid lesions, which otherwise only affects a few percent of the population. These data show that soluble allergens such as flavours and fragrances can cause oral contact allergy.

The monoterpene carvone (l-carvone; Fig. S1a[1]) is the chief component of spearmint oil and is widely used as a mint-flavouring agent (1). The flavour is typically found in oral healthcare products and foodstuffs, such as chewing gum and sweets. In addition to isolation from natural oils, carvone can be synthesized from d-limonene (Fig. S1b[1]) (2) and it is also one of several oxidation products found in auto-oxidized d-limonene (3).

Oral healthcare products are a major source of exposure, and carvone is a constituent of most toothpastes (4, 5). Carvone is considered a weak sensitizer (6) and the prevalence of contact allergy in patch-tested cohorts has been estimated to be 1.6–2.8% (7, 8). A few papers on patients' adverse reactions to carvone or spearmint oil have reported both perioral and intraoral lesions from oral healthcare products, with intraoral lesions described as stomatitis or erosions associated with oral lichen planus (OLP) (9–13). Studies on patients with OLP or oral lichenoid lesions (OLL) have shown an association with carvone or spearmint contact allergy (14–16). However, these reports have not made a clear distinction between OLP, which is considered to be an autoimmune disease, and OLL, such as contact reactions to dental materials or other lichenoid lesions not fulfilling the criteria of OLP (17, 18).

The aim of this retrospective study was to estimate the prevalence of individuals with a positive patch test to carvone in Southern Sweden and to assess the characteristics of this group with regard to other contact allergies and clinical signs with special reference to OLP and OLL.

METHODS

Study population

Data were obtained from a clinical database comprising all patients subjected to patch testing at the Department of Occupational and Environmental Dermatology, Skåne University Hospital in Malmö, Sweden (19). All patients patch-tested with carvone during a 21-year period between 1996 and 2016 were included in the study.

Data recording

Information retrieved from the database included age at time of investigation, sex, type of patch test series in which carvone was included, grading of carvone test reaction and other contact allergies. From patients with a positive carvone patch test, information was also collected regarding the referrer's profession, diagnosis, clinical signs, and localization of signs related to the investigation. It was not possible to deduce from the referrals or patient records whether the patients had OLP or OLL. Therefore, all variants of lichenoid lesions will henceforth be denoted as oral lichen (OL) unless otherwise specified.

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Descriptive and comparative analysis

During the investigated period carvone was used in various patch test series. A descriptive analysis was performed on the collected data of carvone-positive patients regardless of which series they were tested with.

In order to compare the group data of the carvone-positive patients with a more general patch test population, data from the 2 test series with the largest collections of carvone-positive patients, the baseline series (extended) and the dental series (dental patients), were investigated further (Fig. S2[1]). Carvone was included in the Malmö extended baseline series during 1997 to 1998 for research purposes and prevalence assessment. In this paper, "baseline series" will subsequently refer to the extended baseline series. Patch test data from the baseline series were analysed by comparing carvone-positive patients with carvone-negative patients. For the dental series, which included carvone during the whole investigated period, a similar comparison was made between carvone-positive and carvone-negative patients.

In addition, carvone-positive patients within the dental series were compared with a matched group of carvone-negative patients (Fig. S2[1]). The presence of OL, atopy and patch test data were compared. Patients were considered atopic if they had present or previous atopic dermatitis, allergic rhinitis and/or allergic asthma. The matching criteria were sex, age ± 6 years and date of testing ± 3 months except for 2 cases where the criteria were extended to age ± 10 years and date of testing to ± 4 months. Patients were chosen by using a random number generator on sets of patients meeting the required criteria.

The study was performed in accordance with the Declaration of Helsinki.

Patch testing

The patch test method for carvone and other investigated allergens has been consistent throughout the investigated period. Patch testing was carried out using 8-mm diameter Finn chambers (Epitest Ltd Oy, Tuusula, Finland or SmartPractice, Phoenix, AZ, USA) attached to Scanpore tape® (Norgeplaster A/S, Oslo, Norway).

Finn chambers with 20 mg of petrolatum test preparation were applied for 48 h and discarded by the patients themselves. For liquid preparations 15 µl were used, applied to the chambers with a micropipette. Reactions were read on days 3 or 4 and on day 7. Occasional late reactions beyond 7 days were also recorded. Test reactions were graded by an experienced dermatologist according to the International Contact Dermatitis Research Group guidelines (20).

Test preparations of carvone (l-carvone, Acros Organics, Geel, Belgium, CAS: 6485-40-1) were prepared at the Department of Occupational and Environmental Dermatology, Malmö University Hospital, Sweden at a concentration of 5% in petrolatum.

Statistical analysis

The frequencies of the patients' different diagnoses, clinical signs and co-reactivity to different allergens were analysed with the χ^2 test, or with Fisher's exact test when expected values were small. A 2-sided p-value < 0.05 was considered statistically significant.

RESULTS

Of 4,221 referred and patch-tested patients, 147 (3.5%) had a positive test reaction to carvone. The positive reactions were most commonly detected by the dental series, followed by the baseline series and cheilitis series (**Table I**). Complete records were available for 145 patients, whereas 2 only had information on patch test reactions. The mean age at testing was 66.2 ± 11 years. The male-to-female ratio in the carvone-positive group was 1:5.1 compared with 1:2.6 in the carvone-negative group.

Table I. Different test series in which carvone was included and the number of patients with a positive reaction to carvone (with oral lichen (OL) for each series

Test series	Time period	Tested *n*	Carvone-positive[a] *n*	With OL[ab] *n* (%)
Dental series (dental patients)	1996–2016	1,938	99	67 (68)
Baseline series	1997–1998	1,355	14	1 (5)
Cheilitis series	2000–2016	500	9	1 (11)
Dental series (dental personnel)	1998–2016	460	8	1 (13)
Research series (oral lichen)	2006–2008	259	15	11 (73)
Plant series	1996	31	2	0
Cosmetic series	1996	23	0	0
Personal series	n.a.	n.a.	6	2 (33)

[a]Some patients have been tested with more than one test series; [b]number of carvone-positive patients with simultaneous OL.
n.a.: not applicable.

Referring information

Based on the 145 patients with clinical data, the carvone-positive patients were primarily referred by dentists ($n = 99$; 68%), a majority of whom were oral surgeons ($n = 52$; 36%). Physicians referred 36 (25%) of the patients and 10 (7%) patients were enlisted as research subjects in projects on oral lichen. Patients referred by dentists were mainly tested with the dental series (87 of 99), whereas patients referred by physicians were tested with a variety of patch test series.

Diagnoses and clinical signs recorded in the referrals were predominantly localized intraorally ($n = 106$; 73%), whereas the perioral area was affected to a lesser degree ($n = 20$; 14%). Eczema except in the perioral area was present in 34 (23%) patients. Of these, 19 (13%) displayed dermal signs only, i.e. no oral or perioral involvement, often in the form of hand eczema. The main referring inquiry was "contact allergy to dental materials?". Common words used to describe the clinical presentation were "redness", "swelling" or "eczematous". The presence of OL was recorded in 82 (57%) of the patients. OL often coincided with intraoral signs, where 81 of 106 patients had OL, whereas only 5 of the 20 patients with signs from the perioral area had OL. Lichen planus affecting the skin or genital area was recorded in 11 (8%) patients. Patients with OL or intraoral signs were predominantly tested with the dental series, whereas most patients with dermal signs were tested with the baseline series. Most patients with perioral signs were tested with either the dental series or the cheilitis series (**Table II**).

Patch test reactions

The number of positive test reactions to carvone at day 3 and at day 7, respectively, were essentially the same (110 vs. 111) and 31 patients (22%) tested positive only at day 7. Six patients had late reactions, from 10 days

Table II. Diagnoses and clinical signs in carvone-positive patients (*n* = 145) and the proportion of the major patch test series used (dental, baseline or cheilitis)

Clinical diagnosis or symptom	Patients *n*	Patch test series[a] Dental *n*	Baseline *n*	Cheilitis *n*
Diagnosis				
OL (OLP or OLL)	82	68	1	1
Dermal or genital lichen planus	11	5	1	0
Clinical signs				
Oral signs	106	87	2	2
Perioral signs	20	8	1	8
Dermal (no oral or perioral signs)	19	4	11	0

[a]Some of the patients have been tested with more than one test series.
OL: oral lichen; OLP: oral lichen planus; OLL: oral lichenoid lesions.

up to one month after the test application. Two of these patients were re-tested and both showed a reaction on day 3. The test reaction strength (highest strength observed) was "+" in 78 (53%), "++" in 59 (40%) and "+++" in 10 (7%) patients. Besides the 147 patients with a positive reaction, 83 patients had a doubtful reaction to carvone, but no irritant reactions were noted.

Other contact allergies

A majority of the 147 patients had reactions to other allergens ($n = 111$, 76%), most commonly to gold, nickel and mercury (**Table III**(a)). Patients with OL more often had positive reactions to mercury than patients without OL ($p = 0.009$). The mean number of positive reactions to various allergens was 4.1 ± 4.9. The allergens tested were, however, not the same among the carvone-positive patients, since different test series had been used and allergens such as fragrances and acrylates were only included in one or few of the test series. Allergens that gave frequent reactions, but were not tested in the whole group, were spearmint oil, fragrance mix I and balsam of Peru (Table III(b)). Sixteen patients were tested with their private toothpaste and 11 of these displayed a positive reaction (Table III(c)). The tested toothpastes were, for the most part, diluted in water, often at 50% w/v, but several dilutions were often tested, ranging from 5% to 50%, and they varied over the investigated years. Four patients were also tested with undiluted toothpaste. Irritant reactions were noted in 4 patients, of whom 3 were tested with 50% toothpaste and 1 was tested with undiluted toothpaste. No specific brand was singled out as giving more frequent reactions.

Table III. Common positive patch test reactions among the 147 carvone-positive patients

Test substance	Positive reactions/ number of tested	%
(a) Substances that the entire group were tested with (n = 147)		
Gold sodium thiosulphate	52/147	35.4
Nickel sulphate	23/146	15.6
Mercury	20/147	13.6
Potassium dichromate	15/147	10.2
Cobalt chloride	12/146	8.2
Palladium chloride	11/147	7.5
Colophonium	11/147	7.5
Formaldehyde	6/147	4.1
(b) Substances that only part of the group were tested with		
Spearmint oil	55/81	67.9
Fragrance Mix I	23/88	26.1
Balsam of Peru	19/117	16.2
Cinnamal	9/93	8.8
Cinnamyl alcohol	6/68	8.1
Peppermint oil	5/80	6.3
Acrylates[a]	9/125	6.1
Limonene[b]	4/90	4.4
(c) Test with patients' personal toothpaste		
Toothpaste (various brands)	11/16	68.8

[a]Different acrylates grouped together; [b]the preparation of limonene has varied over the investigated years of which some preparations were oxidized.

Comparative analysis of contact allergies within the baseline and dental test series: carvone-positive vs. carvone-negative patients

Carvone-positive patients had significantly higher frequencies of several contact allergies compared with the carvone-negative patients when investigating both series (Table SI[1]). For carvone-positive patients tested with the dental series, positive test reactions to gold and mercury were highly allocated to patients with OL (Table SI[1]).

Positive test reactions to other allergens in the dental series, however, did not differ when comparing the 99 carvone-positive patients to the matched group of carvone-negative patients, but the frequency of OL was significantly higher in the group of carvone-positive patients: 67/99 vs. 28/99 ($p < 0.0001$; **Table IV**).

DISCUSSION

The majority of patients with a positive patch test reaction to carvone were referred for oral or perioral signs, indicating that the main exposure to carvone was from oral healthcare products (5). In addition, OL was prevalent in the studied group, with over half of the patients being affected; an association also seen in previous studies on patients with OL (14–16). Patients with OL

Table IV. Positive patch test reactions in the dental series 1996 to 2016 in carvone-positive patients and a matched carvone-negative group of patients (with oral lichen (OL))

	Dental series – matched groups	
	Carvone-positive (OL) *n* (%)	Carvone-negative (OL) *n* (%)
Number of tested	99 (67)***	99 (28)
Atopy	20 (13)	20 (1)
Patch test reactions to:		
Gold sodium thiosulphate	37 (30)	38 (12)
Palladium chloride	5 (3)	5 (0)
Nickel sulphate	15 (7)	16 (4)
Potassium dichromate	9 (5)	2 (0)
Cobalt chloride	7 (4)	2 (0)
Mercury	18 (16)	12 (9)
Colophonium	6 (3)	3 (1)
HEMA	5 (3)	2 (1)
EGDMA	4 (3)	0 (0)

***$p < 0.001$.
HEMA: hydroxyethyl methacrylate; EGDMA: ethylene glycol dimethacrylate. Significant values are shown for the comparison between the carvone-positive and the carvone-negative group.

were, for the most part, referred by dentists, and patients with dermal signs, such as eczema, were primarily referred by physicians. However, the data may be biased as dentists and physicians are primed to search for clinical signs in different areas. The clinical signs seem also to have raised a suspicion of contact allergy against dental restorative materials rather than rinse-off products, such as dental healthcare products.

A previous study by Paulsen et al. (7) investigated carvone sensitization in patients patch-tested with the baseline series, and found 15 out of 541 (2.8%) consecutively tested patients. The proportion was higher than in the present study, in which 14 patients were positive to carvone out of 1,355 patients (1.0%) tested with the baseline series. When considering all investigated carvone-allergic patients in our study, regardless of test series, the proportion was 3.5% (147 of 4,221), but compared with Paulsen's study in which no clinical relevance was seen in a majority of the patients the presently investigated group seems to have been skewed towards patients with oral or perioral signs. In addition, the mean age was higher in the present study and there was a greater predominance of women among carvone-positive patients, indicating that the sampling may have affected the outcome. The strength of the patch test reactions was similar between the 2 studies, with approximately 50% having a "++" reaction or higher. Paulsen found an association between carvone and Compositae allergy (sesquiterpene lactones), and the reaction to carvone was stronger in patients with both allergies. Of all series investigated in the present study, only the baseline series had sesquiterpene lactone mix included and 11 of 1,355 tested patients had a positive patch test reaction to this. Of the carvone-positive patients, only one patient reacted to sesquiterpene lactone mix.

A positive patch test to carvone on day 7 only was observed in 31 of the 147 patients. This demonstrates the importance of performing more than one patch test reading, since over 20% of the carvone-positive patients would otherwise have been left undiagnosed. Furthermore, 2 of the 6 patients with a late patch test reaction to carvone, day 10 or later, had positive test reactions on day 3 when re-tested. This indicates a possible active sensitization at the initial patch test. However, we have recently observed that carvone-positive patients may show positive reactions as late as 21 days upon re-testing, raising the possibility that a late appearing patch test reaction to carvone may not need to be a sign of active sensitization (to be published).

Overall, the 147 carvone-positive patients showed a high rate of additional contact allergies, especially against metals and fragrance substances (Table III). The high prevalence of spearmint oil sensitization is not surprising, since carvone is the main constituent of spearmint oil (1). Interestingly, a majority of the carvone-positive patients tested with their own toothpaste had a positive test reaction. The toothpastes were of various brands and we do not know what toothpaste constituent the patients reacted to, but most toothpastes contain carvone, though at variable concentrations, as our previous work has shown (4). Sensitization to other flavours found in oral healthcare products, such as peppermint, cinnamal, cinnamyl alcohol and limonene, were not common in the investigated group, but a considerable number of patients had reactions to fragrance mix I and balsam of Peru, which contain flavour substances such as cinnamal and cinnamyl alcohol. Spearmint oil also contains 10–15% limonene (d-limonene) (1), a common fragrant constituent in cosmetic products (21) and also present in toothpastes (4). During a large part of the investigated time period the test preparation of limonene was not intentionally oxidized and it is essentially the oxidation products in limonene that are sensitizers, e.g. carvone (3). Of the carvone-positive patients only 4 of 90 tested with limonene had a positive reaction (Table IIIb) and 2 of these were tested with oxidized limonene. There is also a possibility that patients may have been sensitized to carvone from oxidized limonene, either orally or via the skin, but in a study by Matura et al. only a few patients sensitized to oxidized limonene reacted to carvone in patch tests (22).

It has been shown previously that patch-tested patients with OL often have contact allergies both related to their dental restorations and to carvone (15, 23). The present study also demonstrates a relationship between contact allergy to carvone and metals used in dental restorations. Of the 147 carvone-positive patients studied 55 (35.4%) had a concomitant patch test reaction to gold, and these patients also often had a strong test reaction to carvone. The frequency was comparable to observations on patients with dental gold restorations (24, 25). However, we do not have data regarding the presence of dental materials in the studied group, but the mean number of restorations was probably high, as dental restorations increase with age and the mean age in the group was over 65 years. The 147 investigated patients also had a slightly higher frequency of patch test reactions to mercury (13.6%) compared with studies on dental series tested or patients with OL (15, 26).

Patch test reactions to gold and mercury were more common in carvone-positive patients, when comparing them with all carvone-negative patients tested within the baseline or dental series and the frequency of test reactions was even higher in carvone-positive patients with OL (Table SI[1]). In contrast to what was observed in the unmatched comparative analysis there was no difference in the proportions of contact reactions between the 2 matched groups of carvone-positive and carvone-negative patients tested with the dental series (Table IV). The observed high ratio of women and high mean age in the carvone-positive groups were corrected in the matched comparison. Still, OL was strikingly over-represented

in carvone-positive patients and thus this relationship is neither connected with concomitant contact allergy to gold nor to mercury. Furthermore, regardless of reactivity to carvone, patients with OL in both groups had a high proportion of reactions to mercury.

The oral mucosa differs from the skin, in that it seems to be more tolerant to sensitization and elicitation (27, 28). Still, one must assume that the sensitization route of carvone is primarily through the oral mucosa. Factors that disturb the mucosal environment, such as OL make the oral mucosa more sensitive to external elements and could possibly increase the risk of sensitization (29). Previous studies on oral contact allergy have primarily focused on dental materials, such as acrylates and metals, and only sporadic studies have approached allergy to soluble agents in oral healthcare products, food and beverages. This is especially evident when it comes to lichenoid reactions, although it recently has been shown that contact allergy to fragrances is common among patients with OL (16). The present study demonstrates that contact allergy to carvone is closely related to oral signs and OL, and that oral exposure to carvone is a probable sensitization route.

The authors have no conflicts of interest to declare.

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