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Contact Allergy to Oxidized Linalool and Oxidized Limonene is Over-represented in Individuals with Photocontact Allergy to Ketoprofen

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Simultaneous contact allergies are common in individuals with photocontact allergy to ketoprofen. The rate of contact allergy to the fragrance substances oxidized linalool and oxidized limonene in ketoprofen-photoallergic individuals were investigated in comparison with the corresponding rates in individuals without photocontact allergy to ketoprofen, using Fisher's exact test. A total of 4,021 patients were routinely tested with oxidized linalool; of whom 190 (4.7%) tested positively. For oxidized limonene the numbers were 3,797 patients and 111 positive reactions (2.9%). A total of 19 contact allergic reactions to oxidized linalool were noted in 29 patients (65.5%) who also had photocontact allergy to ketoprofen ($p < 0.0001$). The corresponding figures for oxidized limonene were 10 positive reactions in 24 ketoprofen-photoallergic individuals (41.7%) ($p < 0.0001$). Contact allergy to oxidized linalool and/or oxidized limonene is common in routinely tested patients with dermatitis and, particularly, in those patients who are photoallergic to ketoprofen.

Key words: allergic contact dermatitis; photoallergic; delayed hypersensitivity; fragrance substance; oxidation; patch-testing; photopatch-testing; photosensitizer.

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SIGNIFICANCE

Photocontact allergy to topical ketoprofen is linked to contact allergies to some fragrances. This study investigated the rates of contact allergy to 2 fragrances, oxidized limonene and oxidized linalool, in patients with and without photocontact allergy to ketoprofen. Much higher allergy rates to oxidized substances were detected in patients with photocontact allergy to ketoprofen. Oxidized fragrances are found in a variety of daily life products, therefore an allergy to such substances may have a high impact on one's life. Further studies are needed to determine whether the contact allergies detected lead to actual skin problems.

Photocontact allergy to the non-steroidal anti-inflammatory drug (NSAID) ketoprofen has been reported since the early 1990s (1–13). Topical exposure to ketoprofen can cause severe photoallergic contact dermatitis, which sometimes requires hospitalization in those with photocontact allergy. The photoallergic contact dermatitis can mimic infectious diseases and thrombosis (8).

Patients with a suspected photocontact dermatitis are photopatch-tested at our department in Skåne University Hospital, Malmö, Sweden, but almost always are also tested with our baseline patch-test series with regard to the presence of any contact allergy. When managing patients with photocontact allergy to ketoprofen, a suspicion arose that simultaneous contact allergies to oxidized (ox.) linalool and/or ox. limonene were strong and that they were over-represented in individuals with photocontact allergy to ketoprofen. The aim of this retrospective study was therefore to explore whether this hypothesis was correct.

MATERIALS AND METHODS

Patients

Between 2005 and 2015, 4,050 patients (1,426 males and 2,624 females) were patch-tested because of a suspected allergic contact dermatitis with the Swedish baseline patch-test series to which ox. linalool was provisionally inserted. Similarly, 3,821 patients (1,349 males and 2,472 females) were patch-tested between 2004 and 2015 due to suspected allergic contact dermatitis, with the Swedish baseline patch-test series to which ox. limonene was provisionally inserted. None of the patients with a suspected allergic contact dermatitis was patch- and/or photopatch-tested with ketoprofen. During the periods of routine patch-testing with ox. linalool and ox. limonene, 24 patients tested with both ox. linalool and ox. limonene, and 5 only with ox. linalool, showed positive photopatch-test reactions to ketoprofen (13, 14).

Patch-testing

The Finn chamber technique with the chambers (diameter 8 mm, Smart Practice, Phoenix, Arizona, USA) mounted on Scanpor® tape (Norgesplaster A/S, Oslo, Norway) was used. Chemotechnique Diagnostics in Vellinge, Sweden, manufactured the Swedish baseline series. Petrolatum test preparations with various concentrations of ox. linalool (**Table I**) and ox. limonene (**Table II**) were patch-tested. Initially patch-testing was performed with 4% and 6% ox. linalool containing 0.8% and 1% linalool hydroperoxides, respectively (15–17), and with 3% ox. limonene containing 0.3% limonene hydroperoxides (17–19). These test preparations were made at the Department of Dermatochemistry, Gothenburg University. Since 2012 commercial patch-test preparations of 0.3% limonene hydroperoxides and 1% linalool hydroperoxides from Chemotechnique Diagnostics were used (Table I).

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Table I. Reactions to preparations of oxidized linalool in patients who are ketoprofen-photoallergic (K) and in patients with dermatitis without a diagnosed photocontact allergy to ketoprofen (D)

	Period							
	Feb 2005–Nov 2005		Jul 2006–Jan 2008, April 2010–Nov 2010		July 2012–Dec 2015			
	Concentration (%w/w of linalool hydroperoxides)							
	0.8%[a]		1%[a]		1%[b]		Any preparation	
Group	K	D	K	D	K	D	K	D
Tested, *n*	2	325	17	1,221	10	2,544	29	4,021
Positive, *n*	1	9	11	43	7	139	19	190
+ reactions, *n*	1	6	3	28	5	106	–	–
++ reactions, *n*	0	3	5	13	1	23	–	–
+++ reactions, *n*	0	0	3	2	1	10	–	–
p-value (Fisher's exact test, positive vs negative)	0.060		< 0.001		< 0.001		< 0.001	
p-value (Mann–Whitney)	> 0.3		0.010		> 0.3		–	

[a]Test preparations from the Department of Dermatochemistry, University of Gothenburg. [b]Test preparations from Chemotechnique Diagnostics Vellinge, Sweden.

Petrolatum preparations (20 mg) were applied onto the chambers (20) immediately before application on the patient's back (21). The patches remained under occlusion on the patient's back for 48 h. Test readings took place on days 3 or 4 (D3 or D4) and D7 according to the International Contact Dermatitis Research Group (ICDRG) classification (22, 23).

Photopatch-testing

The Scandinavian photopatch-test series (14), to which ketoprofen was added, and the European baseline photopatch-test series (13) (since 2008), both purchased from Chemotechnique Diagnostics, were used. Seven patients were photopatch-tested exclusively with ketoprofen from one of the above-mentioned series. The Finn chamber technique with the chambers (diameter 8 mm) mounted on Scanpor tape was used. Twenty mg of the petrolatum preparations were applied onto the chambers (20, 21), which were secured on the patient's upper back in duplicate as parallel columns. The patches remained under occlusion for 24 h (13, 24). They were then removed with a minimum of light exposure and with 1 side covered immediately with black cloth. The other side was irradiated with 5 J/cm² broadband ultraviolet A (UVA) (PUVA4000, Photochemotherapy, Herbert Waldmann, Werk für Lichttechnik, Germany). Reading was performed on D3 according to the ICDRG classification (22, 23).

Table II. Reactions to preparations of oxidized limonene in patients who are ketoprofen-photoallergic (K) and in patients with dermatitis without a diagnosed photocontact allergy to ketoprofen (D)

	Period					
	09/2004–11/2005, 07/2006–01/2007, 04/2010–11/2010		07/2012–12/2015			
	Concentration (% w/w of limonene hydroperoxides)					
	0.3%[a]		0.3%[b]		Any preparation	
Group	K	D	K	D	K	D
Tested, *n*	14	1,292	10	2,547	24	3,797
Positive, *n*	4	30	6	83	10	111
+ reactions, *n*	1	16	3	61	–	–
++ reactions, *n*	2	10	2	15	–	–
+++ reactions, *n*	1	4	1	7	–	–
p-value (Fisher's exact test, positive vs negative)	< 0.001		< 0.001		< 0.001	
p-value (Mann–Whitney)	0.25		0.30		–	

[a]Test preparations from the Department of Dermatochemistry, University of Gothenburg. [b]Test preparations from Chemotechnique Diagnostics Vellinge, Sweden.

Statistical analysis

The frequency of contact allergy to ox. linalool in routinely patch-tested patients with dermatitis were compared with the frequency of contact allergy to ox. linalool in patients photoallergic to ketoprofen, using Fisher's exact test, 2-sided. The same comparison was made for ox. limonene. Fisher's exact test, 2-sided, was also used to compare the number of simultaneous reactions to ox. linalool and ox. limonene in the routinely patch-tested patients with dermatitis and those photoallergic to ketoprofen, based on the total number of subjects tested within the respective group, and also based on those within the respective group reacting to ox. linalool and/or ox. limonene. The Mann–Whitney *U* test was used to compare the intensities (+, ++ or +++) of patch-test reactions to ox. linalool and ox. limonene between the 2 groups: individuals with photocontact allergy to ketoprofen and routinely tested patients with dermatitis. A p-value < 0.05 was considered significant.

RESULTS

The contact allergy rates and p-values for the comparisons made are shown in Tables I and II. In 4,021 patients without a known contact allergy to ketoprofen patch-tested with ox. linalool, 190 (4.7%) patients tested positively. The corresponding numbers for ox. limonene were 3,797 patients and 111 positive reactions (2.9%). Nineteen contact allergic reactions to ox. linalool were noted in those 29 patients (65.5%) who were diagnosed with photocontact allergy to ketoprofen during the test period ($p < 0.0001$). The corresponding figures for ox. limonene were 10 positive reactions in the 24 individuals (41.7%) with photocontact allergy to ketoprofen ($p < 0.0001$). The distribution of degrees of patch-test reactivities to ox. linalool and ox. limonene in the group of 24 individuals with photocontact allergy to ketoprofen who were simultaneously patch-tested with both ox. linalool and ox. limonene is shown in Tables I and II. In general, the patients with photocontact allergy to ketoprofen showed more intense reactions to both ox. limonene and ox. linalool than did the patients with dermatitis. However, a statistically significant difference in the degree of reactivity was found only for one of the preparations of ox. linalool tested in the period 2006 to 2010 ($p = 0.010$; Mann–Whitney *U* test, 2-sided) (**Fig. 1**). There was a high degree of concomi-

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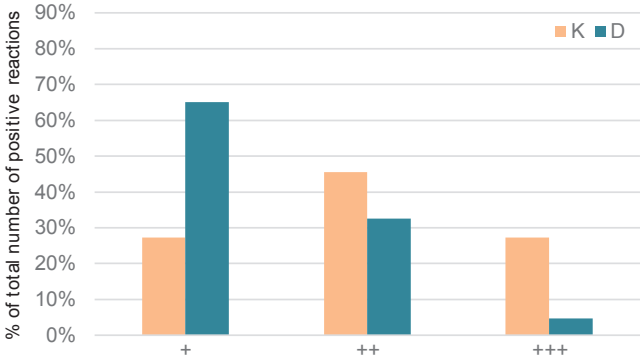

Fig. 1. Distribution of positive reactions to linalool hydroperoxides 1% in petrolatum tested between 2006 and 2010 with regard to degree of reactivity (% of total number of positive reactions scored as +, ++, and +++) in patients with photocontact allergy to ketoprofen (K) and in patients with dermatitis (D).

tant reactions to ox. linalool and ox. limonene in the ketoprofen-allergic patients. In this group 9 of 24 subjects tested with both ox. linalool and ox. limonene tested positively to both. The corresponding figures for the routinely patch-tested patients with dermatitis were 51 of 3,502 ($p < 0.0001$). The same comparison between the 2 patient groups, based on those within respective group reacting positively to ox. linalool and/or ox. limonene, also resulted in a significant difference (9 of 16 vs 51 of 226; $p = 0.0054$) (**Table III**).

DISCUSSION

The results of this study confirmed our clinical suspicion. There was highly statistically significant over-representation of contact allergy to ox. linalool and/or ox. limonene in patients with photocontact allergy to ketoprofen. This over-representation was observed for all preparations of ox. linalool and ox. limonene tested during different periods of time. The clinical impression that the contact allergic reactions to ox. linalool and ox. limonene was stronger in ketoprofen-allergic patients than in routinely tested patients with dermatitis was not confirmed, and, actually, was demonstrated for only one test preparation of ox. linalool used in the period 2006 to 2010 (Tables I and II). In 2011, the over-the-counter distribution of topical ketoprofen was stopped in Sweden, by the Swedish Medical Products Agency, due to a high rate of reported photocontact allergic reactions (www.lakemedelsverket.se). Hence, fewer patients with photocontact allergy to ketoprofen were diagnosed from 2011 (Tables I and II), which might have influenced the possibility of finding a significant difference in degree of reactivity to ox. linalool and ox. limonene between patients with photocontact allergy to ketoprofen and routinely tested patients with dermatitis.

Table III. Patients tested simultaneously with oxidized limonene and oxidized linalool

Test preparation	K	D
Ox. linalool and ox. limonene	9 (38%)	51 (1.5%)
Only ox. linalool	6 (25%)	120 (3.4%)
Only ox. limonene	1 (4.2%)	55 (1.6%)

Number of positive reactions to oxidized linalool and/or oxidized limonene in patients who are ketoprofen-photoallergic (K) and in patients with dermatitis without a diagnosed photocontact allergy to ketoprofen (D)

The reason for over-representation of contact allergy to ox. linalool and/or ox. limonene in individuals with photocontact allergy to ketoprofen is unknown. A possible explanation could be a simultaneous exposure to ketoprofen and linalool and/or limonene. The singlet oxygen produced from excited ketoprofen can oxidize linalool and limonene and form allylic peroxides (25, 26), that may cause sensitization. The allylic hydroperoxides formed are the same as the peroxides expected to be present in ox. linalool and ox. limonene, and their formation is not dependent on an existing photocontact allergy to ketoprofen.

Another possible explanation for the over-representation of contact allergy to ox. linalool is exposure to Orudis® (Sanofi-Aventis AB, Bromma, Sweden), which is one of the most frequently used ketoprofen-containing products for topical use in Sweden (8). Lavender oil, which contains linalool (27), is one of the ingredients in Orudis®. However, the lavender oil used in Orudis® has been photopatch-tested in many patients with photocontact allergy to ketoprofen and Orudis® without any positive reactions (8). It is not known whether the photopatch-tested lavender oil contained any oxidation products of linalool, although studies indicate that the probability is rather high (28–30). Furthermore, limonene is not present in Orudis®. Neither linalool nor limonene were present in the other 2 ketoprofen preparations for topical use distributed in Sweden (Siduro (Meda AB, Solna, Sweden), Zon (Antula Healthcare AB)).

Simultaneous over-representations of various allergies have been reported previously in individuals with photocontact allergy to ketoprofen (2–8, 11, 31). As expected, simultaneous photocontact allergies to benzophenone-based sunscreen agents and fenofibrate are frequent, since all are chemically related to ketoprofen, which is a benzophenone-substituted compound (11). Surprisingly, there are other reported over-represented photocontact allergies that concern chemically unrelated substances, such as fentichlor and tetrachlorosalicylanilide (5–8, 11). In 2014, a study proposed a mechanism to explain why various photocontact sensitizers lead to cross-reactivity in the absence of a chemically related haptenic structure (12). The authors postulated that oxidative tryptophan modification leads to N-formyl-kynurenine, which may continue to react with lysine residues. Many photocontact sensitizers can generate N-formyl-kynurenine by generating UV-induced singlet oxygen, which will oxidize tryptophan.

Contact allergy to *Myroxylon pereirae* and fragrance mix I (FM I) are frequently reported in patients with photocontact allergy to ketoprofen (2, 7, 8, 11). Sur-

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prisingly, it is cinnamic alcohol rather than cinnamal and the other fragrance substances in FM I that is the cause of the reactions to FM I (11, 13, 31). Notably, all simultaneous contact allergy and photocontact allergy in ketoprofen patients reported to date is directed towards aromatic compounds. This seems to be the case also for *Myroxylon pereirae*, which contains many such compounds, including cinnamic alcohol. Unlike these substances, linalool and limonene are terpenes and thus non-aromatic compounds. Furthermore, the oxidation of linalool and limonene is not known to generate aromatic compounds (26, 32–34).

Is there anything special about ox. linalool and ox. limonene with regard to simultaneous allergic reactions? In subjects reacting to ox. linalool and/or ox. limonene, simultaneous reactions to these terpenes were 2.5 times more common in the patients with photocontact allergy to ketoprofen compared with routinely patch-tested patients with dermatitis (9/16 vs 51/226; $p=0.0054$). The results of the current study for the patients with dermatitis who were patch-tested with ox. linalool and ox. limonene correspond to previously published study, in which 25% had had concomitant reactions (17). This difference between the patient groups indicates that the mode of sensitization may differ between the groups. The mechanism of these findings is unknown.

Both oxidized fragrance substances contain sensitizing isomeric hydroperoxides (26, 30, 32–34). Investigations have indicated that contact allergy to a chemically defined hydroperoxide is specific (33, 34). In contrast, it has been hypothesized that skin exposure to hydroperoxides (35) or oxidation products of p- phenylenediamine (36) could trigger positive patch-test reactions by oxidative modifications of skin proteins, such as tryptophan oxidation. This hypothesis (35) has been questioned (37) and was not supported in a retrospective study on patch-tested patients (36). In a recent paper on the contact sensitizers allylic hydroperoxides formed by oxidation of linalool and limonene, the authors investigated possible mechanisms of action focusing on transcription factor Nrf_2 (38).

In subjects with photocontact allergy to ketoprofen there might therefore be plausible explanations for the simultaneous over-representations of photocontact allergic reactions to chemically unrelated photocontact sensitizers (12), but a proven mechanism is still missing to explain the simultaneous contact allergic reactions to chemically unrelated contact sensitizers.

Contact allergy to ox. linalool and/or ox. limonene is common (39–44), particularly in individuals with photocontact allergy to ketoprofen. Independent of the mechanism for induction/existence of the contact allergy to ox. linalool and ox. limonene, as well as the stronger patch-test reactions, from a dermatological point of view, it is the clinical relevance that is important (45). So far, there are only a few case reports (46–48). It is therefore of great interest to further investigate high contact allergy rates to ox. linalool and ox. limonene, but also of utmost importance to investigate skin exposure to ox. linalool and ox. limonene (49, 50). In particular, it is of relevance to establish levels of defined contact sensitizers generated by oxidation of linalool and limonene in consumer products. The role of ox limonene and ox. linalool as rather common contact sensitizers has been discussed in several papers, and their inclusion in testing series has been proposed (51, 52). Two repeated open-application tests have been performed, 1 with ox. linalool (53) and 1 with ox. limonene (54). Further usage tests, based on the highest and still realistic concentrations of ox. linalool and ox. limonene in consumer products, respectively, mimicking daily life exposure as well as being randomized, controlled, and blinded, should be performed. The results of such investigations will help assess whether ox. linalool and ox. limonene are significant clinical contact sensitizers, independent of how the contact allergy has been acquired. Such investigations should also be decisive for the conclusion regarding whether ox. linalool and/or ox. limonene should be considered for inclusion in the European and other baseline patch-test series (52–54).

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