

patients with allergic contact dermatitis (ACD) (1). Fragrance allergy is usually detected by testing with fragrance mix (FM) I, whereas FM II and one of its components, hydroxyisohexyl 3-cyclohexene carboxaldehyde, have been recently added to the European patch test baseline series to increase sensitivity on testing (2).

FM I is a mixture containing eight different components: cinnamyl alcohol, cinnamal, amyl cinnamal, eugenol, isoeugenol, geraniol, hydroxycitronellal, and *Evernia prunastri* extract.

Previous studies have found a significant association between contact sensitization to FM I and contact allergy, or photocontact allergy, to ketoprofen, an arylpropionic acid non-steroidal anti-inflammatory drug (NSAID), which is widely used in Mediterranean countries for topical and systemic administration (3–6).

Concomitant allergy to FM I and ketoprofen may be because of cross-sensitization, particularly involving one FM I component, cinnamyl alcohol (5). Chemical formulas of cinnamyl alcohol and some arylpropionic acid NSAIDs are depicted in Figure 1.

The aim of this study was to assess the frequency of contact and photocontact sensitization to some arylpropionic acid NSAIDs in a series of patients with contact allergy to FM I.

Materials and Methods

Twenty-six patients (21 females and 5 males, aged 18–72 years; mean age, 47.8 years) with positive patch test results to FM I (Firma, Florence, Italy) were evaluated. Reactions were considered relevant in 17/26 patients (65.4%). All subjects were asked to fill in a questionnaire concerning previous or current use of topical and systemic NSAIDs, as well as adverse reactions possibly related to these medications. In such patients, patch tests and photopatch tests were performed with all ingredients of FM I (each at 2% in pet., except for cinnamal tested at 1% in pet.) and the following arylpropionic acid NSAIDs: ketoprofen, fenoprofen, flurbiprofen, ibuprofen, naproxen, and tiaprofenic acid (each at 1% in pet.). All the tested allergens were provided by Firma, Florence, Italy. The same tests were performed in 10 healthy subjects without history of ACD, all being negative to FM I.

Patch tests were applied on the back and occluded for 2 days, using

Finn Chambers® (8 mm; Epitest Ltd, Tuusula, Finland) on Scanpor® tape (Norgesplaster A/S, Vennesla, Norway), and readings were made at D2 and D4. Photopatch tests were carried out by applying the allergens on one side of the back, taking the tape off at 24 hr and exposing them to ultraviolet A (UVA) rays at the dose of 5 J/cm² (UV 801 KL, PUVA/TL01, Photochemotherapy, Herbert Waldmann, Werk für Lichttechnik, Villingen-Schwenningen, Germany), whereas the opposite side of the back was covered with a black cloth. Test reactions were read at 1 and 3 days after irradiation (D2 and D4). The reactions were classified according to International Contact Dermatitis Research Group guidelines.

Results

Test results are summarized in Table 1. Photopatch tests with FM I components and patch tests with NSAIDs gave negative results in all cases. All the tests were negative in control subjects. Four out of 26 patients allergic to FM I had negative patch test results to the single components of FM I, as well as negative photopatch tests to NSAIDs. Among the 22 patients with contact sensitization to at least one FM I component, 12 had positive results to two or more components. As regards photopatch testing with arylpropionic acid NSAIDs, eight patients showed positive results to tiaprofenic acid alone (one subject) or in association with other drugs: ketoprofen (five cases), fenoprofen (one case), and ketoprofen, ibuprofen, and fenoprofen (one case). In all subjects, negative photopatch test results to flurbiprofen and naproxen were observed. Of the nine subjects sensitized to cinnamyl alcohol, seven patients had positive photopatch test results to tiaprofenic acid, with six of them photosensitized also to ketoprofen. All patients reacting to ketoprofen, fenoprofen, or ibuprofen and 7/8 patients reacting to tiaprofenic acid also reacted on patch testing to cinnamyl alcohol, whereas there was no particular association with other fragrance ingredients.

Table 2 summarizes the information regarding the history of use of topical and/or systemic arylpropionic acid NSAIDs in patients photosensitized to at least one of these drugs, as well as adverse reactions related to their use. According to the history, positive photopatch test reactions were considered relevant in only two cases.

Photocontact allergy to arylpropionic acid non-steroidal anti-inflammatory drugs in patients sensitized to fragrance mix I

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Key words: allergic contact dermatitis; cinnamyl alcohol; fragrance mix I; ketoprofen; photoallergic contact dermatitis; tiaprofenic acid.

Fragrance contact allergy is common, affecting a considerable number of

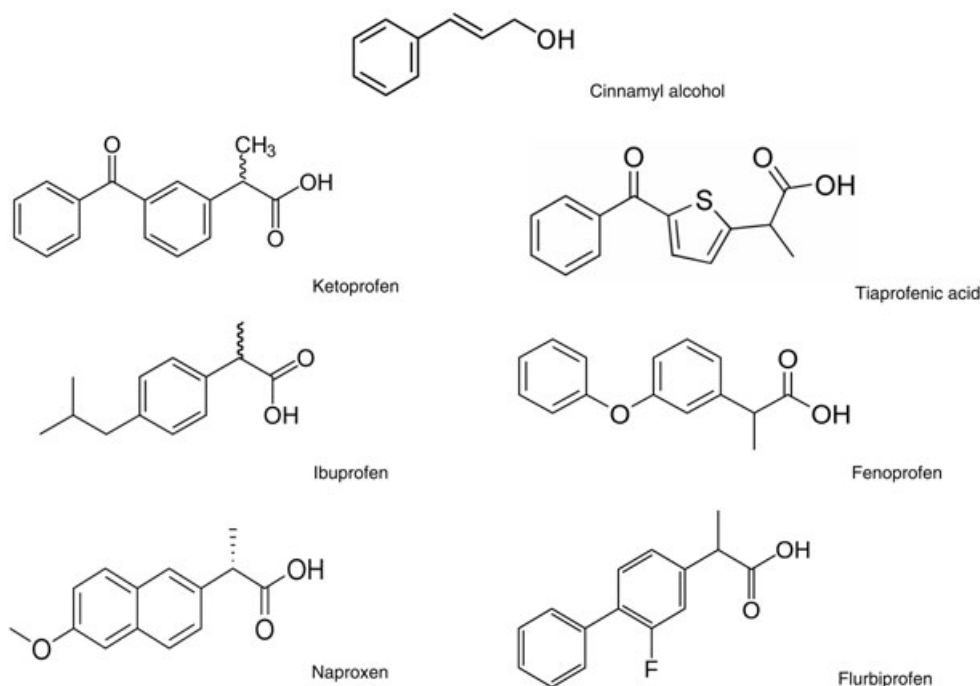


Fig. 1. Chemical structures of cinnamyl alcohol and arylpropionic acid non-steroidal anti-inflammatory drugs (NSAIDs).

Table 1. Test results in 26 patients with contact sensitization to FM I

<i>Patient no.</i>	1	2	3	4	5	6	7	8	9	10	11	12	13	16	17	18	19	21	22	23	25	26	
FM I components (patch test results)*																							
Amyl cinnamal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	++	–	–	–	++	
Cinnamal	++	–	–	–	–	++	–	++	–	++	–	–	–	–	–	++	++	–	–	–	–	–	
Cinnamyl alcohol	–	–	–	–	++	–	–	+++	–	–	+++	–	–	++	++	++	++	–	–	++	–	++	
Eugenol	–	–	++	–	++	–	++	–	–	–	++	–	–	–	–	–	–	–	–	–	–	–	
Geraniol	–	++	–	++	–	–	–	–	–	++	–	–	–	–	–	–	–	–	–	–	–	–	
Hydroxycitronellal	++	++	–	++	–	–	–	–	–	++	–	++	–	–	–	–	–	–	–	–	++	–	
Isoeugenol	–	–	–	–	–	–	–	–	++	–	–	–	–	++	–	–	–	–	++	–	–	–	
<i>Evernia prunastri</i> extract	–	–	–	–	–	–	–	–	++	++	+++	–	++	–	–	–	–	–	–	–	–	–	
NSAIDs (photopatch test results)†																							
Fenoprofen	–	–	–	–	–	–	–	–	–	–	+++	–	–	++	–	–	–	–	–	–	–	–	
Ibuprofen	–	–	–	–	–	–	–	–	–	–	–	–	–	++	–	–	–	–	–	–	–	–	
Ketoprofen	–	–	–	–	++	–	–	–	–	–	–	–	–	++	++	++	–	–	–	++	–	++	
Tiaprofenic acid	–	–	–	–	+++	–	–	–	++	–	++	–	–	+++	++	++	–	–	–	++	–	++	

FM I, fragrance mix I; NSAID, non-steroidal anti-inflammatory drug.

All test results were negative in patient no. 14, 15, 20, and 24. Photopatch tests with flurbiprofen and naproxen gave negative results in all cases.

*Photopatch results for FM components were negative in all cases.

†Patch results for NSAIDs were negative in all cases.

Discussion

Various studies support the association between photocontact allergy to ketoprofen and contact sensitization to FM I (3–6). A strong correlation with sensitization to cinnamyl alcohol has been detected in patients with contact photoallergy to ketoprofen (4). Moreover, among arylpropionic acid

NSAIDs, cross-sensitivity between ketoprofen and tiaprofenic acid has been hypothesized, whereas concomitant reactions with other arylpropionic acid derivatives have been related to simple co-sensitizations (7).

In our series of 26 patients with contact allergy to FM I, the evaluation of photoallergy to arylpropionic acid

drugs showed a high frequency of sensitization to tiaprofenic acid (31%), alone or in combination with other NSAIDs, particularly ketoprofen (23% of the total). As tiaprofenic acid is not available in topical formulation in European countries, the photoreactions to this drug may be explained by cross-reactivity with ketoprofen, which

Table 2. History of use of arylpropionic acid NSAIDs in patients with positive photopatch test results and corresponding drug-related reactions

Patient*	NSAIDs previously used			
	Systemic	Reactions	Topical	Reactions
5	Ibuprofen	None	Ketoprofen	None
9	Ibuprofen, ketoprofen	None	Flurbiprofen	None
11	Ibuprofen	None	—	—
16	Ibuprofen, naproxen	None	Ketoprofen	Mild erythema at site of application
17	Ketoprofen	None	—	—
18	Flurbiprofen, ketoprofen, naproxen, tiaprofenic acid	None	Flurbiprofen, ketoprofen, naproxen	None
23	Ketoprofen	None	—	—
26	Ibuprofen, naproxen	None	Ketoprofen	Hand eczema

NSAID, non-steroidal anti-inflammatory drugs.

*Number reported in Table 1.

is likely to be the true sensitizer in most cases.

When assessing the contact sensitization to single components of FM I, a relevant association appears to exist between allergy to cinnamyl alcohol and photosensitivity to the above-mentioned NSAIDs.

Cinnamyl alcohol is a component of cinnamon spice, which is widely used in both food and fragrances, and is a frequent cause of ACD. The mechanisms responsible for the cross-reactivity between cinnamyl alcohol and ketoprofen are still unknown, although some hypotheses have been proposed, such as structural similarities or formation of common metabolites (4). In a previous study (5), similarities between the two molecules were established using a combined computerized analysis of conformational structure and exposed electrostatic potential surface.

In our case series, all patients with photoallergy to arylpropionic acid NSAIDs previously used at least one of these molecules, either in systemic or topical formulations. However, adverse reactions possibly related to such medications were reported only in two cases after the application of topical ketoprofen, with the occurrence of slight erythema in a patient and hand eczema in the other. The absence of development of adverse reactions after administration of such drugs in sensitive patients might have been because of the lack of concomitant sunlight exposure.

In conclusion, our results suggest that sensitization to cinnamyl alcohol may be considered a marker or even a risk factor of photocontact allergy to ketoprofen and tiaprofenic acid.

Among the arylpropionic acid NSAIDs available in topical forms, naproxen seems to be the safest drug in patients sensitized to cinnamyl alcohol and cross-reacting molecules.

References

1. Nardelli A, Carbonez A, Ottoy W, Drieghe J, Goossens A. Frequency of and trends in fragrance allergy over a 15-year period. *Contact Dermatitis* 2008; 58: 134–141.
2. Bruze M, Andersen K E, Goossens A, ESCD, EECDRG. Recommendation to include fragrance mix 2 and hydroxy-isohexyl 3-cyclohexene carboxaldehyde (Lyal) in the European baseline patch test series. *Contact Dermatitis* 2008; 58: 129–133.
3. Matthieu L, Meuleman L, Van Hecke E et al. Contact and photocontact allergy to ketoprofen. The Belgian experience. *Contact Dermatitis* 2004; 50: 238–241.
4. Girardin P, Vigan M, Humbert P, Aubin F. Cross-reactions in patch testing with ketoprofen, fragrance mix and cinnamic derivatives. *Contact Dermatitis* 2006; 55: 126–128.
5. Foti C, Bonamonte D, Conserva A et al. Allergic and photoallergic contact dermatitis from ketoprofen: evaluation of cross-reactivities by a combination of photopatch testing and computerized conformational analysis. *Curr Pharm Des* 2008; 14: 2833–2839.
6. Devleeschouwer V, Roelandts R, Garmyn M, Goossens A. Allergic and photoallergic contact dermatitis from ketoprofen: results of (photo) patch testing and follow-up of 42 patients. *Contact Dermatitis* 2008; 58: 159–166.
7. Le Coz CJ, Bottlaender A, Scrivener JN et al. Photocontact dermatitis from ketoprofen and tiaprofenic acid: cross-reactivity study in 12 consecutive patients. *Contact Dermatitis* 1998; 38: 245–252.

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