

Allergic and Photoallergic Contact Dermatitis from Ketoprofen: Evaluation of Cross-Reactivities by a Combination of Photopatch Testing and Computerized Conformational Analysis

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Abstract: Allergic contact dermatitis (ACD) and photo-ACD are cell-mediated delayed hypersensitivity reactions of the skin caused by a wide range of substances. Topical ketoprofen (KP), a nonsteroidal anti-inflammatory drug (NSAID), can induce ACD and photo-ACD. Patients with ACD and/or photo-ACD to KP frequently show concomitant sensitization to other substances. The aim of this study was to identify the substances most frequently associated with sensitization to KP, and to evaluate, by means of computerized conformational analysis, whether this association could be due to cross-allergy. 15 subjects with ACD and photo-ACD to KP were tested with the SIDAPA (Società Italiana di Dermatologia Allergologica Professionale ed Ambientale) patch test standard series, including fragrance mix and its components (eugenol, isoeugenol, oak moss, geraniol, hydroxycitronellal, amylcinnamaldehyde, cinnamyl alcohol and cinnamaldehyde) and with the SIDAPA photopatch test series. Allergic reactions to cinnamyl alcohol were noted in all patients, whereas some patients also showed positive reactions to fenciclor, octocrylene and benzophenone-10.

Computerized conformational analysis demonstrated that the structure of cinnamyl alcohol is similar to that of KP, whereas the structures of benzophenone-10, octocrylene and fenciclor are completely different. These results suggest that in patients with contact allergy to KP, concomitant positive reactions to cinnamyl alcohol are due to cross-sensitization, whereas simultaneous allergic reactions to fenciclor, octocrylene and benzophenone-10 should be regarded as co-sensitizations.

Key Words: Allergic contact dermatitis, benzophenone 10, cinnamyl alcohol, cinnamaldehyde, computerized conformational analysis, cross-reactivity, fenciclor, ketoprofen, octocrylene, photo-allergic contact dermatitis.

INTRODUCTION

Allergic contact dermatitis (ACD) is a delayed-type allergic reaction of the skin caused by a wide range of substances, such as metals, resin, cosmetics, jewelry and weeds, including poison ivy or poison oak.

On the first cutaneous contact (induction phase) the organism can respond by developing hypersensitivity; on re-exposure (challenge), as a rule to much lower concentrations than required for initial sensitization, the skin develops an inflammatory reaction that is more and more severe after repeated exposure to an ACD-inducing allergen [1].

Symptoms of ACD are erythema, oedema, vesicles, itching and burning of the skin, followed by crusting, drying and desquamation. The lesions initially occur on areas exposed to a particular allergen; later, in case of persistence of the noxious contact, the lesions may extend to other distant areas.

It is known that irradiation by ultraviolet light results in the activation of some substances into allergens commonly defined as photoallergens. These last substances induce photo-allergic contact dermatitis (photo-ACD), characterized by lesions well demarcated and mostly symmetrical on areas exposed to the light. Although photo-ACD is considered uncommon, many topical photoallergenic culprits have been reported in the literature, the most important of which are sunscreen agents and nonsteroidal anti-inflammatory drugs (NSAIDs). Among the last substances ketoprofen, [(RS)-2-(3'-benzoylphenyl) propionic acid] (KP), is widely used for the treatment of several inflammatory and painful conditions by mouth, rectal, intramuscular and topical routes. In particular, the use of topical KP is currently on the increase thanks to its local analgesic and anti-inflammatory effects and its low toxicity. However, since 1983, an increasing number of case reports of ACD and photo-ACD from KP has been published [2-6]. ACD and photo-ACD to KP develop 1 week to 1 month after the topical use of the drug with an acute erythematous-oedematous and bullous reaction at the site of application and frequently beyond the site of application. Usually the skin eruption clears when the contact with KP ceases. Occasionally, however, the patient develops lesions even after removal of the drug, and some times may present

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recurrent transient or persistent light reactions due to retention of the molecule in the epidermidis [7, 8]. Residual hyperpigmentation or intractable leukomelanoderma may occur [9].

The diagnosis of ACD and photo-ACD with KP is made by means of patch and photopatch test. Photoirradiation must be performed using UVA radiation (5 J/cm² or less based on the minimal erythral dose) for the reason that the action spectrum of KP is predominant in the UVA range [1, 10]. Patients with ACD and photo-ACD to KP rarely develop photo-allergy with other anti-inflammatory drugs with an aryl propionic acid structure, such as alminoprofen, fenoprofen, flurbiprofen, ibuprofen and naproxen [10]. On the other hand, they frequently show allergic reactions to substances with a benzophenone group, such as benzophenone-3, fenofibrate, amiodarone, tiaprofenic acid and suprofen [10]. In addition, lots of patients react to fragrance mix (FM) [11].

CROSS- REACTIVITY

Contact simultaneous positive reactions may be due to co-sensitization or cross-reactivity among substances with similar chemical structure. A definite distinction between cross-reactivity and co-sensitization is usually detected by means of animal experiments where the exposure factor can be strictly controlled. Knowledge in humans is based on statistical analysis of patch test data and theoretical speculations; however, there is no standardized way of differentiating with sureness between the two phenomena, since it is often difficult to obtain accurate information on previous exposure.

AIM OF THE STUDY

In presence of multiple contact allergic reactions the key problem is to establish if they are due to cross-reactivity or co-sensitization.

Simultaneous positive reactions between KP and other benzophenone-derivative substances have been reported in literature [3, 6]. On the other hand, contemporaneous contact sensitivity to KP and FM is so frequent to induce to think that the association is not fortuitous [11, 12].

Aim of this study was to identify substances most frequently associated with sensitization to KP, and to evaluate, by means of computerized conformational analysis, whether this association could be due to cross-allergy or co-sensitization.

PERSONAL DATA

Between October 2006 and May 2007 we studied 15 patients (6 women, 9 men), aged 21-68 years (mean, 42.1 years), with eczematous dermatitis from KP-containing gels. Among these patients, 6 had used Lasonil[®] gel and 6 Fastum[®] gel, both containing 2.5% KP, whereas 3 had applied Artrosilene[®] gel, containing 5% KP.

The patients were tested at least 3 months after complete disappearance of the dermatitis. Patch and photopatch tests were performed with the SIDAPA (Società Italiana di Dermatologia Allergologica Professionale ed Ambientale) photopatch test standard series (FIRMA Diagent, Florence, Italy) (Table 1) and the above mentioned KP-containing gels

as is. Photo-patch tests were carried out by applying the allergens on one side of the back and leaving them under occlusion for 2 days; readings were performed at 48 and 96 h (D2 and D4). Simultaneously, photopatch tests were carried out by applying the allergens on the other side of the back, taking the bandages off at 24 h and exposing them to UVA rays at the dose of 5 J/cm² (UV 801 KL, PUVA/TL01, Photochemotherapy, Herbert Waldman, Werk für Lichttechnik, 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).

All 15 patients were also patch tested with FM and its components (eugenol, isoeugenol, oak moss, geraniol, hydroxycitronellal, amylcinnamaldehyde, cinnamyl alcohol (Calc), cinnamaldehyde (Cald)) (Table 2) and with Myroxylon pereirae (Euromedical, Calolziocorte, Lecco, Italy).

The reactions were classified according to International Contact Dermatitis Research Group (ICDRG) guidelines.

The software used was Trydent V1.0.0 (Molecular Modeling for Medicinal Chemists) from Wavefunction, Inc. (18401 Von Karman Avenue, Suite 370 – Irvine, CA 92612 U.S.A.). With this software, all the structures resulting more frequently positive to patch and photopatch tests were studied. Graphic representation of the molecular structures is possible thanks either to a search of the database program provided, or by drawing them with the instruments supplied by the same program. Once the molecule has been drafted, it is firstly optimized by the 'Best Conformer' function, which shows the most probable three-dimensional configuration. Successively, the other likely existing configurations (shapes in space) for the same molecule are visualized by the 'Good Conformer' function. Both functions use a molecular calculation mechanism and the MMFF (Merck Molecular Force Field). They perform the calculation in the first case for the lowest-energy shape of the molecule, while in the second case they provide a selection of all the possible low energy shapes (configurations). In all these steps, windows can be opened that describe some physico-chemical properties of the base molecule and of its possible configurations. Such properties may change according to the molecular configurations e.g. the Strain Energy (in Kj/mol), the dipole moment (in Debye units) and other properties.

In the next stage the possible configurations, or just some of them, are processed with the Structure/Property function. This allows the calculation and visualization of various other molecular properties, namely: electron density, exposed electrostatic potential surface, electrostatic potential map, potential local ionization map. The methods used for these computations are based on three well-documented quantum chemical models that are suitable and practical for the calculation of the structure (geometry) and properties of organic molecules, i.e. PM3 (semi-empirical molecular orbital), 3-21G and 6-31G* (Hartree-Fock molecular orbital). Put simply, the key difference between the three models is the degree of approximation and the amount of data used to process the properties. The molecular property we used to highlight those elements shared by the different molecules studied is the Exposed Electrostatic Potential (EEP) surface. This representation is a composite of three different surfaces: an electron density surface depicting the overall molecular size and

Table 1. Results of Patch and Photopatch Tests with KP-Containing Gels and with the SIDAPA Photopatch Test Series in 15 Patients with Eczematous Reactions from KP-Containing Gels

Allergens	Positive Patch Tests N. of Patients (%)	Positive Photopatch Tests N. of Patients (%)
2-Ethylhexyl-4-dimethylaminobenzoate (Eusolex 6007) 10% pet.	0	0
2-Hydroxy-4-methoxybenzophenone (Eusolex 4360) 10% pet	0	1 (6.7)
2-Phenylbenzimidazole-5-sulphonic acid (Eusolex 232) 10% pet.	0	1 (6.7)
4-Aminobenzoic acid 10% pet.	0	1 (6.7)
Benzophenone-10 (mexenone) 10% pet.	2 (13.3)	3 (20)
Benzophenone-4 10% pet.	0	0
Bithionol 1% pet.	0	1 (6.7)
Butyl methoxydibenzoyl-methane (Eusolex 9020) 10% pet.	0	0
Diethylhexylbutamidotriazone 10% pet.	0	0
Fenticlor 1% pet.	0	4 (26.7)
Homosalate 10% pet.	0	0
Isoamyl p-methoxycinnamate (Neoheliopan E100) 10% pet.	0	1 (6.7)
KP 2.5% pet.	3* (20)	12 (80)
KP-containing gels, as is	3* (20)	12 (80)
Meroxyl XL (drometrisole trisiloxane) 10% pet.	0	0
Octocrylene 10% pet.	0	3 (20)
Octylmethoxycinnamate (Eusolex 2292) 10% pet.	0	0
Piroxicam 10% pet.	0	1 (6.7)
Sesquiterpene lactone mix 0.1% pet.	0	1 (6.7)

* 1 patient with contact allergy and 2 with photoaggravated contact allergy.

shape, a negative electrostatic potential surface identifying the electron-rich regions and a positive electrostatic potential surface identifying the electron-poor regions. Regions that are respectively electron-rich or poor are known to be preferential reactive sites for nucleophilic reactions. Similarities in the quantity of electrical charge (electrons) in otherwise different molecules may lead to a similar reactivity to proteins. We considered a lack of symmetry of the molecules, associated to electron charges separation in different parts of the same molecule, as an orientation tool directing the molecules toward the reactive site of proteins. The dipole momentum considers the distance between the opposite poles of a molecule (i.e. the electron-rich and electron-poor parts) and the intensity of the respective electrical charges.

The results of the patch and photopatch tests are reported in Tables 1 and 2.

The patch tests elicited 2+ positive reactions to KP and KP-containing gels in 3 patients (20%), 2 of which had photoaggravated contact allergy. Photopatch tests with KP and KP-containing gels revealed a strong (3+ positive reactions) contact photoallergy to KP in 12 patients (80%). The reactions were relevant in all the cases.

Table 2. Results of Patch Tests with FM and its Constituents and Myroxylon Pereirae in 15 Patients with Eczematous Reactions from KP-Containing Gels

Allergen	Positive Reactions No. of Patients (%)
FM 8% pet.	10 (66.7)
Amylcinnamaldehyde 2% pet.	0
Geraniol 2% pet.	0
Isoeugenol 2% pet.	1 (6.7)
Oak moss 2% pet.	0
Eugenol 2% pet.	2 (13.3)
Cinnamaldehyde 1% pet.	1 (6.7)
Cinnamyl alcohol 2% pet.	15 (100)
Hydroxycitronellal 2% pet.	0
Myroxylon pereirae	5 (33.3)

Of the 15 patients patch tested with FM and Myroxylon pereirae (balsam of Peru), 10 (66.7%) had positive reactions to FM (with relevance in 6 cases), and 5 of them were simultaneously positive to Myroxylon pereirae (33.3%). 2+ ($n = 3$) and 3+ ($n = 12$) allergic reactions to Calc were noted in all patients (100%), whereas only 1 subject (6.7%) had a positive reaction to Cald. Moreover, 3 patients (20%) showed a contact photoallergy to octocrylene, 4 (26.7%) to fenciclor, 3 (20%) to benzophenone-10, while 2 (13.3%) showed contact allergy to benzophenone-10.

Application of the 'Good Conformer' processing system to KP and Calc (Figs. 1 and 2) shows that, in both molecules, there are few possible, identical, high-energy molecular

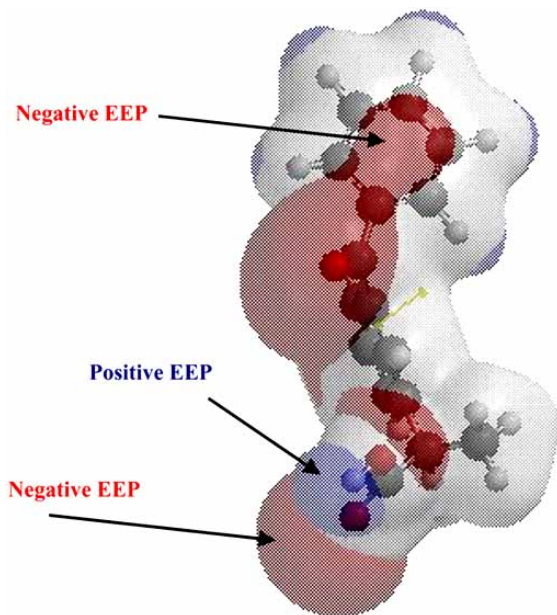


Fig. (1). KP: this structure represents one of the high-energy conformers and its Exposed Electrostatic Potential.

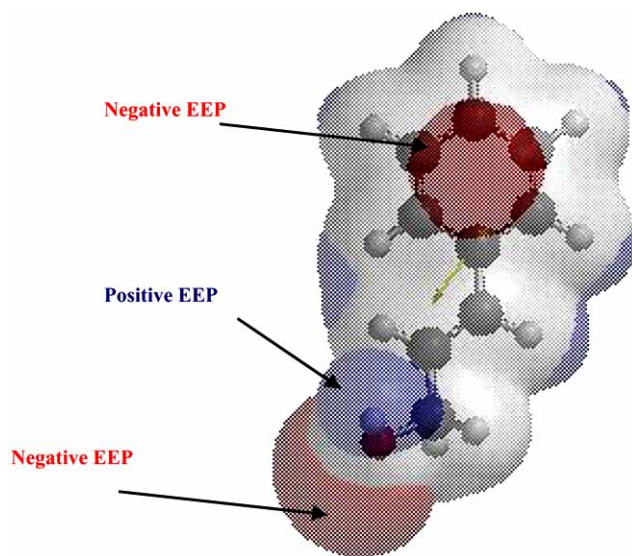


Fig. (2). Cinnamyl alcohol: this structure represents the low-energy conformer and its Exposed Electrostatic Potential.

structures, accounting for a total of 9 structures including the stable one. The two molecules increase the 'dipole momentum' by the same amount (+10%), going from the standard status to the highest-energy structure. The amount of energy needed to shift the KP molecule from the lowest-energy conformer to the high-energy conformer has been calculated to be about 9 kJ per mole, which is comparable to the amount of energy provided by UVA rays in the photopatch testing procedure (5 J/cm²). Moreover, in the case of Calc, the amount of energy necessary to shift from the lowest-energy conformer to the high-energy conformer is similar to that of KP (6 kJ/mole). The EEP presentation of KP revealed that the molecule, which is a bi-aromatic ketone, has a concrete possibility of delocalization of the electron clouds which lie above and below the two benzene (phenyl) rings and of the electrons shared in the double C=O bond in the ketone group. All such electrons form a molecular electron cloud that is shifted in the direction of the ketone oxygen atom, the most electronegative atom in the molecule. This type of shift can also take place, albeit with some difficulty, in the direction of the carboxyl group that is in 'para' position (in the low-energy, non excited, structure), as this group is separated by a carbon atom from the benzene ring. Indeed, the EEP presentation shows some electron cloud accumulation also on the oxygen of the carboxylic group.

Calc, which is a simpler molecule than KP, nevertheless has a similar structure to that of KP. The double bond external to the phenyl ring is conjugated with the phenyl group, and therefore capable of inducing delocalization of the electron cloud. The EEP presentation of Calc reveals that the molecule has the possibility of delocalization of the electron clouds which are above and below the benzene (phenyl) rings and of the electrons shared in the C=O bond in the alcohol group.

In the case of Cald, its structure is much more polarizable (shifting of the electron cloud) than that of Calc, thanks to the presence of a carbonyl group attached to the alpha-beta double bond (Fig. 3). Analyzing the Cald structure, the possible configuration of the molecule in which the carbonyl

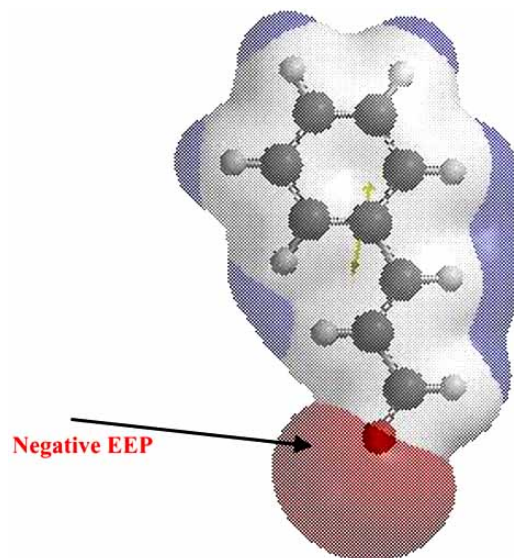


Fig. (3). Cinnamaldehyde: this structure represents the low-energy conformer and its Exposed Electrostatic Potential.

group attracts all the electrons is highly likely. Nevertheless, this structure, which is even more evident in the UV-excited configuration, is completely different from the Calc and KP structures.

The results of the computerized conformational analysis of benzophenone 10, octocrylene and fenticlor (Figs. 4-8) are discussed below.

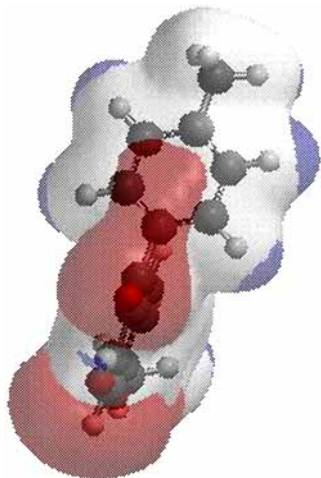


Fig. (4). Benzophenone-10: this structure represents one of the high energy conformers and its Exposed Electrostatic Potential.

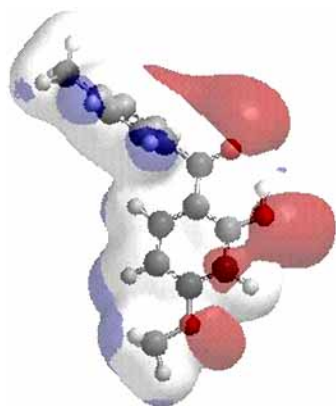


Fig. (5). Benzophenone-10: this structure represents another one of the high-energy conformers and its Exposed Electrostatic Potential.

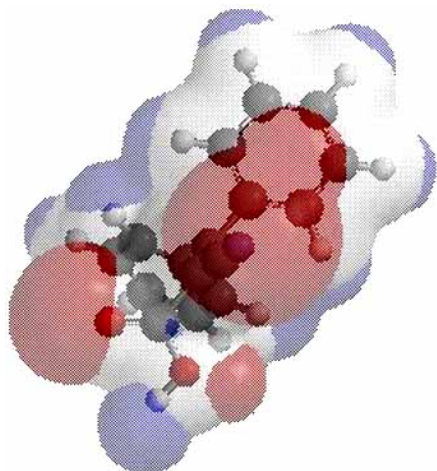


Fig. (6). Hydrolyzed octocrylene: this structure represents the lowest energy conformer and its Exposed Electrostatic Potential.

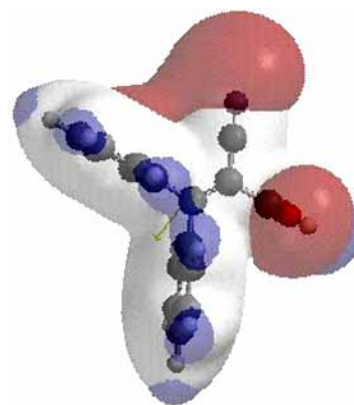


Fig. (7). Hydrolyzed octocrylene: this structure again represents the lowest energy conformer, in this case rotated in order to show similarities with fenticlor and benzophenone-10 and its Exposed Electrostatic Potential.

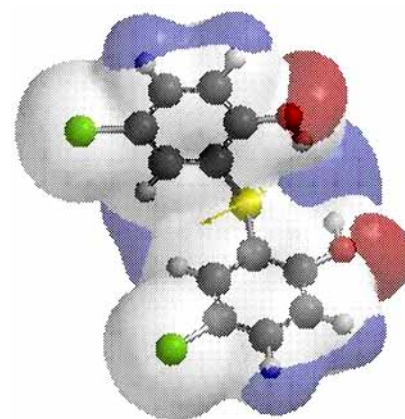


Fig. (8). Fenticlor: this structure represents the only high-energy conformer and its Exposed Electrostatic Potential.

DISCUSSION

Topical KP is an arylpropionic acid derivative used to relieve pain and inflammation in the muscles, tendons and joints. Several case reports of ACD and photo-ACD from topically administered KP have been published [2-6]. Previous studies have shown that patients with contact allergy to KP had a high prevalence of simultaneous positive reactions to FM [3, 11]. Concomitant reactions to KP and FM, however, cannot be explained by the presence of fragrances among the constituents of the KP-containing gels [6]. Another study disclosed the occurrence of simultaneous reactions to KP and Cald in many patients, hypothesizing that an aldehyde group near a benzene ring could induce sensitization and cross-reaction between the two substances [11]. However, a recent study performed in 8 patients with contact and photocontact allergy to KP who were tested with FM components disclosed positive reactions to Cald in all patients, whereas only 5 of them reacted to Cald [10]. In agreement with the results obtained by Girardin *et al.* [12], in a series of 15 patients with contact or photocontact allergy to KP, only 1 patient (6.7%) had a positive reaction to Cald, while all the patients were simultaneously sensitized to Cald, evidencing a strong association between the two substances suggestive of cross-sensitization. Durbize *et al.* [13] attributed this cross-sensitivity to the high reactivity induced by the association of a benzene ring with an oxygen.

The goal of this study was to ascertain whether conformational analysis of the substances that resulted positive in our series of patch and photopatch tests could clarify the reasons for these simultaneous reactions.

Firstly we took into account the lowest energy structure of Calc (Fig. 2) and one of the 9 possible high-energy structures of KP (Fig.1) which can be predicted to form during exposure of the patch to UV rays. We noted the subsequent events.

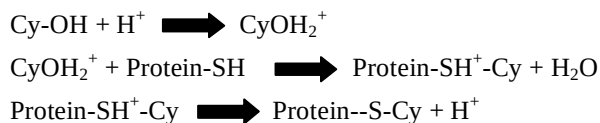
- 1) Both structures present two distinct sites with negative EEP. The two sites correspond, one to the carbonyl group (acid for KP and alcohol for Calc) and the other to a phenyl ring (in the case of KP, the electron cloud tends to shift toward the ketone oxygen, but still remains attached to the phenyl ring).
- 2) In both structures, a part bearing a positive charge is inserted in the same plane and position between the two negatively charged sites: it corresponds to the acidic hydrogen in KP and the alcohol hydrogen in Calc.

These shared characteristics allow us to hypothesize a similar electronic reactivity for the two structures. Therefore, this strengthens the likelihood that in case of a chemical attack to protein macromolecules, the two structures will not be identified as different.

For its strong negative polarization on the oxygen atom, Calc can: a) be attracted by electron deficient atoms; b) easily acquire an ubiquitary hydrogen ion (H^+). The resulting H_2O^+ group bound to the cinnamyl residue is an optimum leaving group, as reported in the chemical literature. H_2O will successively detach and R^+ (cinnamyl cation) would react with the negatively polarised groups of proteins. More probably, this happens with a concerted (contemporary) mechanism, which does not lead to the real formation of the free cation.

As N-acetyl-S-(1-phenyl-3-hydroxypropyl) cysteine and another cysteine derivative have been identified in the urine of rats fed with Calc [14], the most probable binding site of the R^+ ion, in our opinion, could be represented by the sulfidryl group of protein cysteines.

The H^+ ion is then released again. The suggested concerted mechanism is the following:



Therefore, we consider Calc as a true hapten which does not need any transformation in order to bind to the proteins of the skin.

Cald (Fig. 3) has a powerful allergenic potential, and its structure is much more polarizable than that of Calc, because of the 'electron sucking' effect of the $C=O$ group, channelled to the phenyl ring via the double bond, which is in the alpha-beta position of the carbonyl group. This situation (a carbonyl group attached to an alpha-beta double bond) is common to many allergens.

So, why is Cald not found to frequently cross-sensitize with KP and/or Calc? The possible configuration of the molecule where the carbonyl group attracts all the electrons

is highly likely, but such an electron withdrawal would be so complete that the phenyl ring would completely lack negative charges. This structure, which is even more evident in the UV excited state, is completely different from the Calc and KP structures and naturally presents a different reactivity.

Some of our patients with contact or photocontact allergy to KP showed positive reactions to fenticlor, octocrylene, and benzophenone-10. Benzophenone-10, which is widely used in sunscreens, shows a somewhat different electronic distribution (Fig. 4) from those of Calc and UV-excited KP. Much the same can be said of octocrylene, a substance contained in suncare and cosmetic preparations, which has rarely been reported as a cause of photo-ACD [15]. The octocrylene molecule has a more expanded distribution of electrons than KP and Calc and, in all its possible (more than 100) conformations, the electron cloud distributions display no relevant differences. Indeed, the amount of energy required to convert octocrylene into the most unstable conformation is higher than that of sunrays. In fact, the electrons polarization increases dramatically only when the molecule has lost its alkyl chain, for instance by acid hydrolysis, which gives rise to just two conformations. Therefore, the reactive form is made available only after an enzymatic or acidic attack on the skin. However, conformational analysis suggests that even the hydrolyzed form of octocrylene (Fig 6), like benzophenone-10, is different from Calc and UV-excited KP. In other words, if we take Calc as the standard structure, we find a strong similarity with the excited KP structure and much weaker similarities with benzophenone-10 and hydrolyzed octocrylene. In view of its frequent presence in flavourings, spices, foods and perfumes, it seems likely that Calc is the real sensitizer among the above molecules (100% of patients). These findings suggest that positive reactions to octocrylene or benzophenone-10 in patients sensitized to Calc and KP may be simultaneous reactions rather than cross-sensitizations, explainable by the frequent use of sun care products (which may contain octocrylene or benzophenone-10) [6].

Fenticlor is a chlorophenolic compound with an antifungal activity. In our case series, only 4 (26.7%) patients had contact photoallergy to fenticlor, which was instead reported by Vigan *et al.* [16] in 80% of patients photoallergic to KP. A possible explanation for such a different prevalence could be the absence of fenticlor in the topical preparations marketed in Italy. In the case of fenticlor, it has a very complex structure (Fig. 8) which does not allow an easy interpretation of its possible configurations. Conformational analysis shows that no structural similarities exist between fenticlor and either KP or Calc, while there are evident similarities between fenticlor and hydrolyzed octocrylene or benzophenone-10 (Figs. 5 and 7), in which the EEP presentation of hydrolyzed octocrylene and benzophenone-10 is shown from a different point of view.

In conclusion, our preliminary results appear to suggest that in patients with contact allergy to KP, concomitant positive reactions to Calc are due to true cross-sensitization, whereas positive reactions to KP, Cald, benzophenone-10, octocrylene and fenticlor should be regarded as co-sensitizations. On the basis of these results of a combination

of computerized conformational elaboration and clinical study, it would seem that cross-allergy may occur among molecules with common characteristics, such as little freedom to modify their spatial structure (the molecule has a fixed shape), polarization sites (electron enrichment and depletion), and similarities among the number, distribution and chemical structure of the reactive parts of the molecule.

ABBREVIATIONS

ACD	=	Allergic contact dermatitis
Calc	=	Cinnamyl alcohol
Cald	=	Cinnamaldehyde
EEP	=	Exposed Electrostatic Potential
FM	=	Fragrance mix
ICDRG	=	International Contact Dermatitis Research Group
KP	=	Ketoprofen
MMFF	=	Merck Molecular Force Field
NSAID	=	Nonsteroidal anti-inflammatory drug
SIDAPA	=	Società Italiana di Dermatologia Allergologica Professionale ed Ambientale
UVA radiation	=	Ultraviolet A radiation

REFERENCES

References 17-19 are related articles recently published.

- [1] Czarnobilska E, Obtulowicz K, Wsolek K. Type IV of hypersensitivity and its subtypes. *Przegl Lek* 2007; 64: 506-8
- [2] Drieu C, Marguery MC, Giordano-Labadie F, Journe F, Loche F, Bazex J. Photoaggravated contact allergy and contact photoallergy caused by ketoprofen: 9 cases. *Ann Dermatol Venereol* 2001; 128: 1020-4.
- [3] Matsushita T, Kamide R. Five cases of photocontact dermatitis due to topical ketoprofen: photopatch testing and cross-reaction study. *Photodermatol Photoimmunol Photomed* 2001; 17: 26-31.
- [4] Matthieu L, Meuleman L, Van Hecke E, Blondeel A, Dezfoulian B, Constandt L, *et al.* Contact and photocontact allergy to ketoprofen. The Belgian experience. *Contact Dermatitis* 2004; 50: 238-41.
- [5] Hindsen M, Zimerson E, Bruze M. Photoallergic contact dermatitis from ketoprofen in southern Sweden. *Contact Dermatitis* 2006; 54: 150-7.
- [6] Devleeschouwer V, Roeladts 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: 159-66.
- [7] Sugiura M, Hayakawa R, Kato Y, Sugiura K, Hashimoto R. 4 cases of photocontact dermatitis due to ketoprofen. *Contact Dermatitis* 2000; 43: 16-9.
- [8] Nakazawa T, Shimo M, Chikamatsu N, Igarashi T, Nagata O, Yamamoto M. Study on the mechanism of photosensitive dermatitis caused by ketoprofen in the guinea pig. *Arch Toxicol* 2006; 80: 442-8.
- [9] Nabeya RT, Kojima T, Fujita M. Photocontact dermatitis from ketoprofen with an unusual clinical feature. *Contact Dermatitis* 1995; 32: 52-3.
- [10] Le Coz CJ, Bottlaender A, Scrivener JN, Santinelli F, Cribier BJ, Heid E, *et al.* Photocontact dermatitis from ketoprofen and tiaprofenic acid: cross-reactivity study in 12 consecutive patients. *Contact Dermatitis* 1998; 38: 245-52.
- [11] Pigatto P, Bigardi A, Legori A, Valsecchi R, Picardo M. Cross-reactions in patch testing and photopatch testing with ketoprofen, thiaprofenic acid, and cinnamic aldehyde. *Am J Contact Dermatitis* 1996; 7: 220-3.
- [12] Girardin P, Vigan M, Humbert PF. Cross-reactions in patch testing with ketoprofen, fragrance mix and cinnamic derivatives. *Contact Dermatitis* 2006; 55: 126-8.
- [13] Durbize E, Vigan M, Puzenat E, Girardin P, Adessi B, Desprez PH, *et al.* Spectrum of cross-photosensitization in 18 consecutive patients with contact photoallergy to KP: associated photoallergies to non-benzophenone-containing molecules. *Contact Dermatitis* 2003; 48: 144-9.
- [14] Delbressine LP, Klippert PJ, Reuvers JT, Seuttlter-Berlage F. Isolation and identification of mercapturic acids of cinnamic aldehyde and cinnamyl alcohol from urine of female rats. *Arch Toxicol* 1981; 49: 57-64.
- [15] Madan V, Beck MH. Contact allergy to octocrylene in sunscreen with recurrence from passive transfer of a cosmetic. *Contact Dermatitis* 2005; 53: 241-2.
- [16] Vigan M, Girardin P, Desprez P, Adessi B, Aubin F, Laurent R. Photoallergie au kétoprofène et photosensibilisations au tétrachlorosalicylanide et au Fenticlor®. *Ann Dermatol Venereol* 2002; 129: 1125-7.
- [17] Fylaktakidou KC, Hadjipavlou-Litina DJ, Litinas KE, Varella EA, Nicolaides DN. Recent developments in the chemistry and in the biological applications of amidoximes. *Curr Pharm Des* 2008; 14(10): 1001-47.
- [18] Giovannetti A, Pierdominici M, Di Iorio A, Cianci R, Murdaca G, Puppo F, *et al.* Apoptosis in the homeostasis of the immune system and in human immune mediated diseases. *Curr Pharm Des* 2008; 14(3): 253-68.
- [19] Isolauri E, Kalliomaki M, Laitinen K, Salminen S. Modulation of the maturing gut barrier and microbiota: a novel target in allergic disease. *Curr Pharm Des* 2008; 14(14): 1368-75.

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