

Spectrum of cross-photosensitization in 18 consecutive patients with contact photoallergy to ketoprofen: associated photoallergies to non-benzophenone-containing molecules

E. DURBIZE¹, M. VIGAN², E. PUZENAT¹, P. GIRARDIN², B. ADESSI², PH. DESPREZ¹, PH. HUMBERT¹, R. LAURENT² AND F. AUBIN¹

¹Photodermatology Unit and ²Allergy Unit, Department of Dermatology, University Hospital, 2 Place Saint-Jacques, 25030 Besançon cedex, France

Contact photoallergy to ketoprofen gels has been widely reported, and cross-sensitivity reactions with other compounds, such as tiaprofenic acid, fenofibrate and benzophenones, are well known. However, positive photopatch tests to other different non-benzophenone-related compounds have recently been observed. We report the results of photopatch testing in patients with contact photoallergy to ketoprofen and discuss the spectrum of cross-sensitization to ketoprofen. 18 consecutive patients with a history of photocontact dermatitis from ketoprofen were investigated. Patch and photopatch tests were performed. As expected, we observed positive photopatch tests to Ketum* gel and ketoprofen 2.5% in petrolatum in all patients (100%). However, it was remarkable to note positive photopatch tests to other unexpected and non-relevant allergens, including fenchlor (67%), tetrachlorosalicylanilide (28%), triclosan (17%), tribromsalan (11%) and bithionol (11%), with no clinical relevance. Interestingly, these agents belong to the family of halogenated salicylanilides and related compounds, which have been forbidden in Europe since the 1970s. Our results raise the question of hyper-photosusceptibility to non-relevant allergens induced by photosensitivity to ketoprofen. The mechanism may involve the high photoreactivity induced by the association of a benzene ring with an oxygen group.

Key words: benzophenone; halogenated salicylanilides; hyper-photosusceptibility; ketoprofen; medicaments; photosensitivity. © Blackwell Munksgaard, 2003.

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Ketoprofen is a 2-arylpropionic acid derivative among non-steroidal anti-inflammatory drugs, that was made by Rhone-Poulenc SA (Anthony, France) in the late 1960s and first sold in an oral form in the early 1970s. Since 1983, several cases of allergic and photoallergic contact dermatitis from ketoprofen gel have been reported in Italy and Spain (1). In France, the drug has been available for topical application since 1989, the first cases of photocontact dermatitis having been described in 1996 (1). Worldwide, there are now many drugs containing ketoprofen, such as a poultice, gel, tape, cream, oral medicine and injection. Several cases of contact and photocontact allergy to topical ketoprofen have been described. In addition, cross-reactivity to fenofibrate and benzophenones and risk of prolonged photosensitivity are well known (2, 3). Photo-

allergy is due to the benzophenone moiety of ketoprofen (double benzene rings linked by a ketone group, Fig. 1) rather than to the arylpropionic function. This induces cross-reactivity to fenofibrate and benzophenone-3 but not to arylpropionic acid derivatives without a benzophenone moiety (2). Furthermore, the presence of the benzoyl ketone group seems important for the photosensitivity reaction because this group is not present in other fibric acid analogues (4). However, positive photopatch tests to other different non-benzophenone-related compounds have recently been observed in patients with photocontact dermatitis from ketoprofen (5). We have reported similar cases in a previous preliminary study (6), and we now report the results of photopatch testing in 18 consecutive patients with photocontact allergy to ketoprofen and

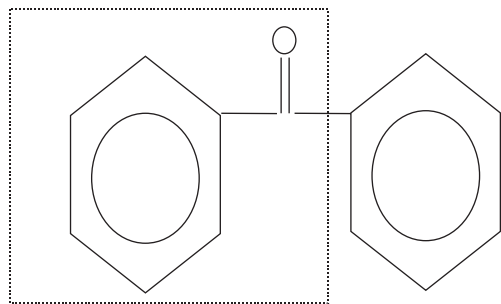


Fig. 1. Chemical structure of benzophenone (double benzene rings linked by a ketone group) showing within the square a benzoyl radical (benzoyl ketone).

discuss the spectrum of cross-sensitization to ketoprofen.

Materials and Methods

Patients

18 consecutive patients with a history of photocontact dermatitis from ketoprofen were investigated in our department between June 1998 and June 2002. Among them, 11 had been already retrospectively investigated (6). They were 14 women and 4 men, aged 21–59 years (mean 31.6 years), of Fitzpatrick's skin types II to IV. 13 patients developed a pruritic, papulovesicular eruption while 5 patients experienced a bullous eruption. Dermatitis appeared 8–10 days after application of ketoprofen. The cutaneous lesions were localized to non-sun-exposed application areas and then to all photoexposed areas in 14 patients and to sun-exposed application areas in 4 cases. History showed prolonged photosensitivity in 3 cases for more than 1 year after withdrawal of ketoprofen.

Light sources

Photobiological testing was performed with polychromatic irradiation (1000 xenon light, Dermolum UM-W*, Muller, Moosinning, Germany) filtered with a Schott WG 305 filter and a high-pressure metal halide UVA lamp (UVA 700L, Waldmann, Reichstett, Germany). Irradiance was measured by Centra* UV (Osram, Munich, Germany). The total spectrum radiant energy was 3.0 mW/cm² and that of UVA 80 mW/cm². We previously investigated the minimal erythema dose (MED) in 50 normal healthy subjects with different skin types (II to IV) to evaluate the normal value induced by the solar simulator used in our department. When this value is under 300 mJ/cm², we consider that the patient demonstrates photosensitivity because the MED

of all the normal subjects tested is well over this value (unpublished data).

Patch and photopatch testing

Patch and photopatch tests were performed in triplicate with the French Society of Photodermatology standard series, Ketum gel* (Laboratoires Ménarini, Rungis, France), ketoprofen 2.5% in white petrolatum (pet.), Surgam* (tiaprofenic acid) 30% dispersion of the tablet in pet. and Lipanthyl* (fenofibrate) 30% dispersion of the tablet in pet. The UVA sunscreens included: Anthelios XL60* (Mexoryl XL), octyl dimethyl para-aminobenzoic acid (PABA) 10% pet., phenylbenzimidazole sulfonic acid 10% pet., benzophenone-4 10% pet., butyl methoxydibenzoylmethane 10% pet., octyl methoxycinnamate 10% pet., 4-methylbenzylidene camphor 10% pet., PABA 10% pet. (provided by Chemo Technique Diagnostics, Tygelsjö, Sweden), isoamyl-*p*-methoxycinnamate 10% pet. and benzophenone-3 10% pet. (provided by Trolab, Reinbek, Germany). The patches were removed after 24 h. One set was then irradiated with 10 J/cm² of UVA and a second set was irradiated with a suberythema dose of total spectrum (0.75 MED). The third non-irradiated set served as the patch test control. Patch and photopatch test reactions were read at 24 h and 48 h after irradiation. Grading of positive reactions (+ to +++) was made according to the International Contact Dermatitis Research Group recommendation (7).

Results

Total spectrum MED was decreased in 3 patients while remaining within normal limits (normal value >300 mJ/cm²) in 12 patients (not performed in 3 patients). There was no immediate urticarial reaction after polychromatic or UVA irradiation. Positive patch tests and photopatch test results are summarized in Table 1. As expected, we observed positive photopatch tests with Ketum* gel and ketoprofen 2.5% pet. in all patients (100%). Photopatch testing with Ketum* gel demonstrated UVA and total spectrum photoaggravated contact allergy (PACA) in 4 patients and a UVA contact photoallergy (CPA) in 14 cases. Photopatch testing with ketoprofen 2.5% pet. demonstrated 2 PACAs and 16 CPAs. In addition, we observed positive photopatch test with fenofibrate in 13 out of 18 cases (13 CPA), with tiaprofenic acid in 11 out of 18 cases (11 CPA) and with benzophenone-3 in 6 out of 18 cases (6 CPA). However, it was remarkable to note positive photopatch tests with other unexpected allergens, including fentichlor (67%),

Table 1. Positive results of patch and (PT) photopatch tests after irradiation by solar simulator (UVB) and UVA

Allergen	PT	UVB	UVA	Percentage of patients with positive photopatch test (n = 18)
Ketum* gel	4	14	14	100 (18; 4 PACA, 14 CPA, 4 CA)
Ketoprofen 2.5%	2	14	16	100 (18; 2 PACA, 16 CPA, 2 CA)
Fenofibrate	1	9	13	72 (13; 13 CPA, 1 CA)
Tiaprofenic acid	0	7	11	61 (11; 11 CPA)
Benzophenone-3	0	0	6	33 (6; 6 CPA)
Fentichlor	0	8	12	67 (12; 12 CPA)
Fragrance mix	5	7	10	83 (15; 5 CA, 2 CPA; 8 PACA)
Tetrachlorosalicylanilide	0	0	5	28 (5; 5 CPA)
Neuriplège*	0	4	5	28 (5; 5 CPA)
Chlorpromazine	0	0	3	17 (3; 3 CPA)
Triclosan	1	1	2	17 (3; 1 CA, 2 CPA)
Promethazine	0	0	3	17 (3; 3 CPA)
Bithionol	0	0	2	11 (2; 2 PA)
Tribromsalan	0	0	2	11 (2; 2 CPA)
Isoamyl- <i>p</i> -methoxycinnamate	0	0	2	11 (2; 2 CPA)
Hexachlorophene	0	0	2	11 (2; 2 CPA)
Chlorhexidine	1	0	1	6 (1; 1 CA, 1 CPA)

CA, contact allergy; PACA, photoaggravated contact allergy; CPA, contact photoallergy. Neuriplège* was dispersed at 10% in petrolatum.

tetrachlorosalicylanilide (28%), triclosan (17%), tribromsalan (11%) and bithionol (11%). No clinical relevance was found for these unexpected positive photopatch tests, except for chlorhexidine which had previously been used, as recognized by the patient. Phototesting with Mexoryl XL was negative in all cases (0 out of 18).

Discussion

Contact photoallergy to ketoprofen gels has been widely reported since their introduction (1, 8). A recent study conducted by the French drug surveillance system detected 337 cases since 1989, and analysis has shown a frequency of cutaneous adverse events (essentially photosensitization and contact allergy) from 0.008/1000 to 0.023/1000 applications (8). In addition, cross-sensitivity reactions with other molecules, such as tiaprofenic acid, fenofibrate and benzophenones, and the risk of prolonged photosensitivity are well known (2, 3). These results led the National Commission of the French drug surveillance system to

require a modification underlining these risks on the packaging of ketoprofen gels.

As a 2-arylpropionic acid derivative, ketoprofen is a benzophenone inducer. Photoallergy to ketoprofen is due to the benzophenone moiety, which includes a benzoyl radical. The presence of the benzoyl ketone group (Fig. 1) seems important for the photosensitivity reaction (4) and explains the different cross-photoreactions with molecules sharing this group. However, positive photopatch tests to other different non-benzophenone-related compounds have recently been observed in patients with photocontact dermatitis from ketoprofen (5, 6), suggesting another mechanism. In our study on 18 consecutive patients with CPA to ketoprofen, we also found positive photopatch tests to unexpected allergens, including fentichlor (67%), tetrachlorosalicylanilide (28%), triclosan (17%), bithionol (11%), tribromsalan (11%) and hexachlorophene (11%). In our study, we think that the possibility of an angry back syndrome can be excluded because the positive photopatch tests were distant from each other and separated

Table 2. Previous results of photopatch testing in patients with ketoprofen contact photoallergy

Allergen tested	Le Coz et al. [n = 18 (%)]	Martin et al. [n = 22 (%)]	Durieu et al. [n = 19 (%)]	Present Study [n = 18 (%)]
Fenofibrate	67	72	100	78
Tiaprofenic acid	100	100	100	61
Benzophenone-3	25	63.5	21	33
Fragrance mix	33	NT	68	83
Fentichlor	NT	45	10	67
Tetrachlorosalicylanilide	NT	22.5	5	28
Triclosan	NT	NT	26	17
Hexachlorophene	NT	NT	5	11
Tribromsalan	NT	NT	NT	11

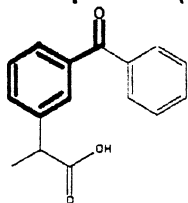
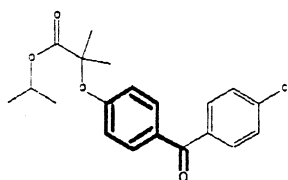
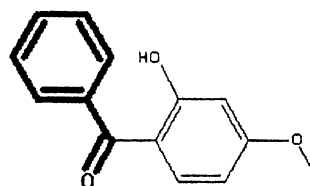
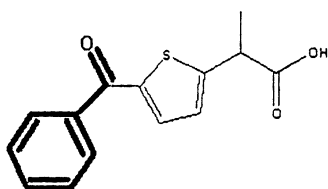
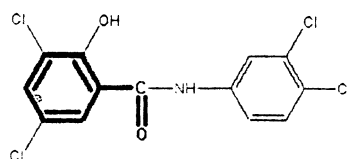
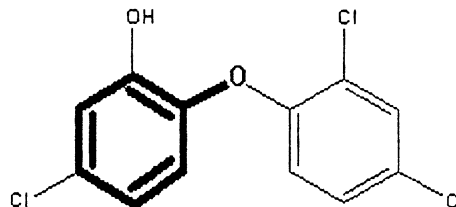
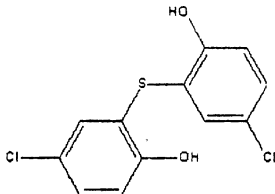
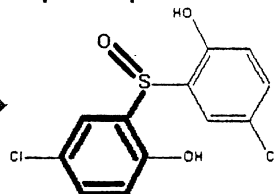
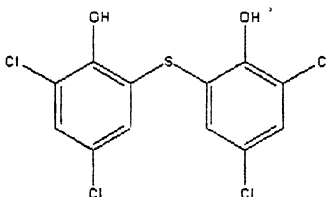
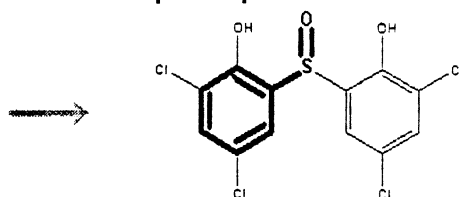
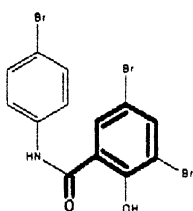
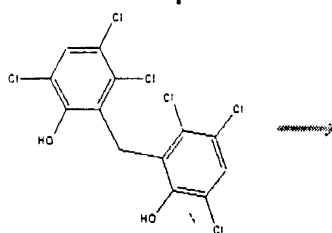
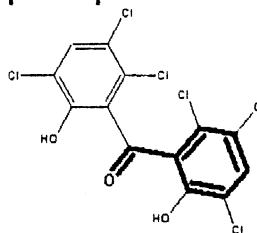
kétoprofen (Ketum^R)**fenofibrate****benzophenone-3****tiaprofenic acid****tetrachlorosalicylanilide****triclosan****fentichlor****photoproduct****bithionol****photoproduct****tribromsalan****hexachlorophene****photoproduct**

Fig. 2. Structural formulae of ketoprofen, benzophenone-related agents, halogenated salicylanilides and related compounds.

by areas of normal skin. Our results thus confirm our preliminary findings (6) of unusual photo-reactions in patients photoallergic to ketoprofen.

Contact photoallergies to non-benzophenone-containing molecules in patients with photodermatitis from ketoprofen have previously been reported (Table 2). In a series of 19 patients, Durieu et al. (5) observed positive photopatch tests to fentichlor (10%), tetrachlorosalicylanilide (5%), triclosan (26%) and hexachlorophene (5%)

compared to 67%, 28%, 17% and 11% respectively, in our study. More recently, in a series of 22 patients with CPA to ketoprofen, Martin et al. (9) found positive photopatch tests to fentichlor and tetrachlorosalicylanilide in 45% and 22.5% respectively compared to 67% and 28% in our study. To our knowledge, no other data are available in the literature, but most studies on CPA to ketoprofen did not investigate cross-reactions between non-benzophenone-related compounds.

Interestingly, these agents belong to the family of halogenated salicylanilides and related compounds, which were widely used between 1960 and 1970 as antimicrobial agents by various manufacturers in soaps and cosmetics (10–12). It is remarkable to note that these molecules have been prohibited in Europe since the 1970s because of their responsibility for an epidemic-like outbreak of contact photodermatitis and the development of chronic actinic dermatitis or persistent photosensitive states (13–18). In addition, the personal histories of our patients did not support the relevance of these positive photopatch tests, except for chlorhexidine. It is thus unlikely that our patients have been sensitized with these molecules. Furthermore, in the last 20 years of our photopatch testing experience, we did not observe any positive photoreaction with halogenated salicylanilide and related compounds (tetrachlorosalicylanilide, bithionol, fenticlor, tribromsalan and hexachlorophene). It is thus very surprising to rediscover young patients with positive photopatch tests to these old compounds with no clinical relevance.

Our results raise the question of an acquired hyper-photosusceptibility to non-relevant allergens induced by photosensitivity to ketoprofen. As for photocontact dermatitis from halogenated salicylanilides, it may also be suggested that ketoprofen acts as a primary photoallergen which subsequently induces photoreactivity to secondary photoallergens (14).

Photosensitivity includes both phototoxic and photoallergic reactions. Phototoxicity of ketoprofen involves the production of free radicals following photoperoxidation of linoleic acid in cellular membranes and DNA damage with single-strand break and formation of pyrimidine dimers (19). Photoallergy involves a cell-mediated hypersensitivity response and occurs only in previously sensitized individuals. Finally, the chemical structure and the variety of chemical reactions may explain the high frequency of photosensitivity reactions to ketoprofen. The reasons for a hyper-susceptibility to develop multiple photosensitivities after photosensitization to ketoprofen are not known, but it should be noted that all these molecules share a benzene ring linked to an oxygen group (Fig. 2). The oxygen group is included within the benzoyl ketone group, except for triclosan where oxygen is within a phenoxy group. It may thus be suggested that the association of a benzene ring and an oxygen group is highly photoreactive (4). To our knowledge, there is no other example of such a hyper-photosusceptibility induced by a drug, and it may be a specific characteristic of ketoprofen. However,

the association of a benzene ring and an oxygen group is not specific for ketoprofen, and further studies are required to explain the induction of hyper-photosusceptibility by this agent.

Altogether, these data emphasize the need for further investigation of patients with contact photosensitivity to ketoprofen, who remain at high risk of multiple contact photoreactions not always related to the benzophenone moiety. In addition, pharmacists and physicians should inform patients of the risk of multiple photoreactions when using a ketoprofen gel and photoprotection should be thus recommended.

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Address:

François Aubin

Department of Dermatology

2 Place Saint-Jacques

25030 Besançon cedex

France

Fax: 33 3 81 21 81 63

e-mail: francois.aubin@ufc-chu.univ-fcomte.fr