

Photocontact dermatitis from ketoprofen and tiaprofenic acid: cross-reactivity study in 12 consecutive patients

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The arylpropionic acid derivatives (APADs) ketoprofen and tiaprofenic acid can provoke photoallergic dermatitis. Possible cross-reactivity between APADs is of importance in patients using non-steroidal anti-inflammatory drugs. Because of the similarities in chemical structures, we investigated patients with photoallergy to ketoprofen or tiaprofenic acid, in order to study cross-reactivity between APADs and a possible pattern of cross-reactivity between benzophenone-containing molecules, so as to determine the molecular basis of photoallergy to ketoprofen or tiaprofenic acid. 10 patients with photoallergy to topical ketoprofen, 2 with photoallergy to oral tiaprofenic acid, and 15 control subjects with no history of contact dermatitis from APADs, nor from benzophenone-containing molecules, were photopatch tested in triplicate with ketoprofen, tiaprofenic acid, other APADs (alminoprofen, fenoprofen, flurbiprofen, ibuprofen and naproxen), benzophenone-containing molecules (fenofibrate, oxybenzone, sulisobenzon), and unsubstituted benzophenone. 1 set was irradiated with UVA light, 1 with solar-simulated irradiation and 1 dark control. Tests were read at 2, 3 and 4 days. Patients reacted to both ketoprofen and tiaprofenic acid (12/12), fenofibrate (8/12), oxybenzone (3/12) and unsubstituted benzophenone (11/12), but not to other APADs, nor to sulisobenzon. Tests remained negative in control patients. Photoallergy is due to the benzophenone moiety of ketoprofen, or to the very similar thiophene-phenylketone of tiaprofenic acid, but not to their arylpropionic function. This induces cross-reactivity to fenofibrate and oxybenzone but not to APADs without a benzophenone moiety, which may therefore probably be used in such patients. Unsubstituted benzophenone should be added to standard phototesting series.

Key words: photoallergic contact dermatitis; cross-sensitivity; non-steroidal anti-inflammatory drugs; ketoprofen; tiaprofenic acid; arylpropionic acid derivatives; benzophenone; photopatch testing technique. © Munksgaard, 1998.

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List of abbreviations:

APAD: arylpropionic acid derivative; KP: ketoprofen; MED: minimal erythematous dose; NSAID: non-steroidal anti-inflammatory drug; TA: tiaprofenic acid; TS: total spectrum; UVA: ultraviolet A; UVB: ultraviolet B.

Among non-steroidal anti-inflammatory drugs (NSAIDs), systemic and topical 2-arylpropionic acid derivatives (APADs) have been widely used in recent years. Some are available in topical forms and represent an attractive alternative to systemic use as effective treatments in localized musculoskeletal diseases, but they have a potential for contact sensitization. APADs, especially ketoprofen

(KP) and tiaprofenic acid (TA), have frequently been reported as responsible for allergic and photoallergic contact dermatitis (1–9). Although they are uncommon, cross-reactions between APADs (Table 1) have sporadically been described (7, 10–14), but systematic study of cross-reactivity has rarely been performed in such patients. However, possible cross-reactions are of importance, because athletes or patients with chronic rheumatic diseases frequently use topical and systemic NSAIDs. Cross-reactions to fenofibrate (4, 15) have also occasionally been reported in patients with photoallergy to KP. It has been postulated (15) that the photoallergic mechanism involves the benzophenone structure, which is common to the

Table 1. Cross-reactions between APADs reported in the literature

	Contact dermatitis	Photocontact dermatitis
ibuprofen	ibuproxam (10) fenoprofen & flurbiprofen (11)	naproxen (11)
ketoprofen	ibuproxam (7, 10, 11) ibuproxam & flurbiprofen (12)	tiaprofenic acid (11, 12) ibuproxam (7, 11) flurbiprofen (12) tiaprofenic acid & suprofen (13) tiaprofenic acid & flurbiprofen (14)

2 molecules. We have investigated patients with a history of photocontact dermatitis from topical KP or systemic TA, based on a comparison of chemical structures (16). To investigate the molecular basis of photoallergy to KP and TA, we looked for a possible pattern of cross-reactivity between various APADs available in topical or systemic forms, unsubstituted benzophenone, and benzophenone-containing molecules.

Patients and Methods

Patients

12 consecutive patients with a history of acute eruption on photoexposed areas, induced by KP or TA, were investigated in the Contact Allergy Unit, Department of Dermatology of Strasbourg (France), between January 1996 and August 1997. They were 7 women and 5 men, aged 17 to 76 years (mean 43.5 years), of Fitzpatrick's skin types II to IV (17). The first 2 patients had systemic photocontact dermatitis after oral intake of TA 100 mg 2× a day (Sur-gam®, Laboratoires Roussel, Puteaux, France). Both had applied topical KP (Kétum gel®, Laboratoires Ménarini, Rungis, France) before, with a history of photocontact dermatitis in the 2nd case. The vesiculobullous lesions started within 24 h of sun exposure and involved photoexposed areas. The other 10 patients suffered from acute photocontact dermatitis after application of topical KP, Kétum gel® in 9 cases, and Profénid gel® (Laboratoires Roussel, Puteaux, France) in 1 case.

Patch testing and phototesting

The patients were tested at least 1 month after the end of their acute episode of contact dermatitis, with the Finn Chamber technique. Each patient was tested on the upper back with the revised (18) European standard series (Trolab®, Hermal, Reinbek, Germany) and with their own ointment, Kétum gel® or Profénid gel® as is, placed in 8-mm Finn Chambers mounted on Scanpor® tape (Epitest Ltd, OY, Finland). The patches were removed after 2 days and the reactions were assessed 20 min later, and again after an additional 1 and 2 days.

The positive reactions were graded as + to +++, as recommended by the International Contact Dermatitis Research Group (19).

For ultraviolet (UV) irradiation, 2 sources of light were used, so as to achieve irradiation with UVA alone and with both UVA and UVB. Solar-simulated UV irradiation was provided by a 1000 W Xenon lamp (Dermolum UM-W®, Müller, Moosinning, Germany). The lamp was filtered with a 1-mm WG 305 filter to remove UVC (<290 nm) and attenuate the UVB (290–320 nm) emission to that approximating sunlight. A metal halide lamp was added, in order to enhance release of UVA and UVB. Spectral irradiance of the filtered light was measured with a dosimeter (Horiba) included in the equipment, and a computer (Amstrad) regulated the light delivery. By using this UV source, the minimal erythematous dose (MED) of the skin on the mid-to-upper back was determined for each patient 24 h after irradiation, as the lowest dose of polychromatic light at which clearly demarcated erythema was observed. As a UVA (320–400 nm) source, we used a PUVA irradiation unit (Tecimatic®, Dixwell®, Lyon, France) with a fluorescent bulb (Philips HPA). The lamp was filtered to attenuate UVB emission. The integrated irradiance of the lamps at the skin surface was determined with an UVA–365 broad band radiometer (Dixwell®, Lyon, France). A total dose of 10 J/cm² UVA was emitted during a 5-min period.

For subsequent phototesting, patch and photopatch tests were performed in triplicate on the upper and middle back of the patients, using allergens placed in 8-mm Finn Chambers mounted on Scanpor® tape. The allergens comprised the patient's own topical ointment (Kétum gel® or Profénid gel®), the individual constituents of Kétum gel® (kindly provided by Laboratoires Ménarini) and some of Profénid gel® (Trolab®). They included lavender oil 2% in white pet., neroli oil 2% pet., parabens 3% pet., the excipients of Kétum gel® (diethanolamine, carbomer 940 and ethanol) as is, and triethanolamine 2.5% pet. (Trolab®). The APADs series comprised alminoprofen (kindly provided by Laboratoires du Docteur E. Bouchara, Levallois-Perret, France) 5% and 1% pet., fen-

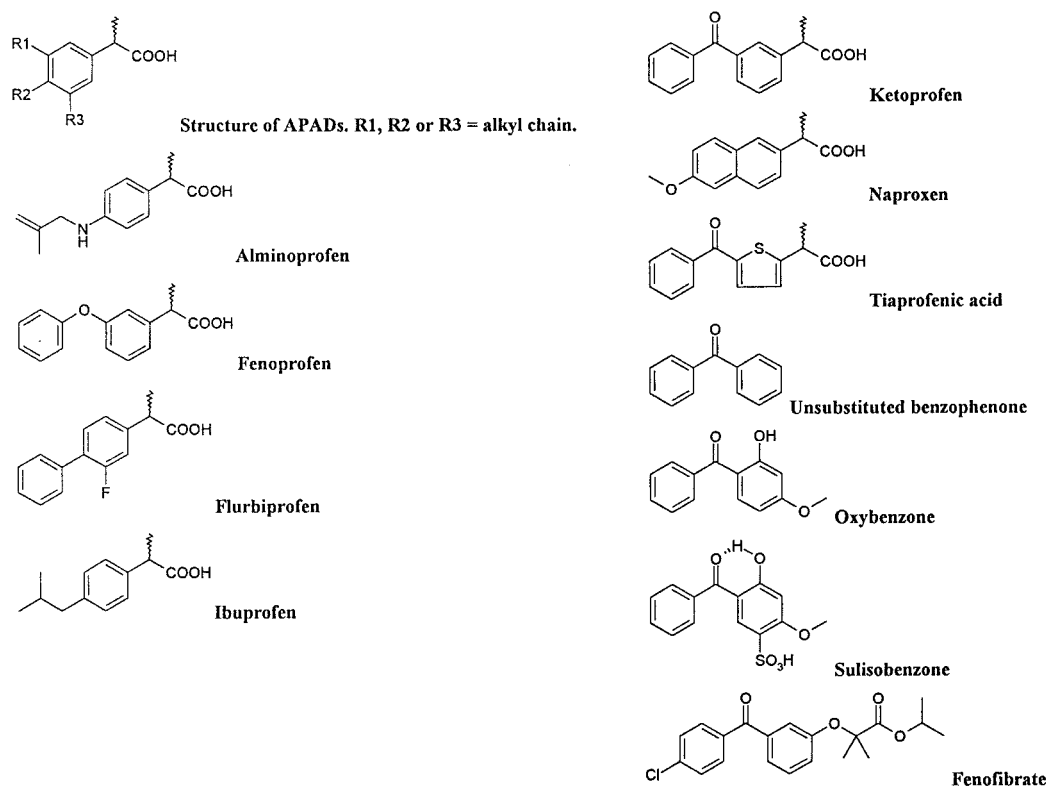


Fig. 1. Structure of arylpropionic acid derivatives (APADs) and of benzophenone-containing molecules (16, 31). Hydrogen bond is present for sulisobenzonate but not for oxybenzone.

oprofen 5% and 1% pet., flurbiprofen (kindly furnished by Laboratoires Knoll S.A, Valenciennes, France) 5% and 1% pet., ibuprofen 5% and 1% pet., KP (kindly provided by Laboratoires Ménarini) 2.5% and 1% pet., naproxen 5% pet. and TA 1% pet. We also tested the benzophenone-derivative molecules (Fig. 1) fenofibrate 10% pet., oxybenzone (Eusolex 4360) 10% pet. (Trolab[®]) and sulisobenzonate (benzophenone -4) 10% pet. (Trolab[®]), and unsubstituted benzophenone (Fluka Chemie, assay >99%) 1% pet. 2 sets of patches were removed after 1 day. Immediately afterwards, 1 set was irradiated with 10 J/cm² of ultraviolet A (UVA), and the 2nd set was irradiated with a suberythematous dose of polychromatic light (75% MED). When 1 of the 2 areas was being irradiated, the other was completely covered. The 3rd set served as dark control and was removed after 2 days. Patch and photopatch test reactions were read at 1, 2, 3 and 4 days after irradiation. Grading of positive reactions (+ to +++) was made according to the International Contact Dermatitis Research Group recommendations (19).

Control subjects

We tested KP (1% pet.), TA (1% pet.), fenofibrate (10% pet.) and unsubstituted benzophenone (1%

pet.), in addition to a sunscreen series, in 15 patients with suspicion of polymorphous light eruption or photocontact dermatitis unrelated to these molecules, and who had never used topical NSAIDs. The control subjects gave their approval after oral explanations. Patch tests were applied in triplicate on the back of the patients and irradiated as above.

Results

Major clinical data are reported in Table 2. None of the patients had used oral TA before the acute episode, but most of them reported oral intake of KP, ibuprofen or other NSAIDs. 1 patient (case no.11) had previously been treated with fenofibrate some years ago. Most of them commonly used perfumed, counterirritant or muscle relaxing ointments, after post-traumatic symptoms. The standard series showed at least 1 positive patch test in each patient (Table 3). The most frequently positive tests were nickel sulfate in 5 cases, balsam of Peru in 4 cases, and fragrance mix in 4 cases. 4 patients (case nos. 1, 6, 9 and 12) had multiple sensitivities.

Photopatch test results are summarized in Table 3. In the 2 patients with systemic photocontact dermatitis from TA, photopatch tests with this

Table 2. Clinical details of the 12 patients. K: Kétum gel® and P: Profénid gel®

Patient no./ ointment used	Sex/age (years)	Indication for topical ketoprofen	Delay of appearance after onset of treatment	Duration of disease	Phototype	Sports player
1/K	M/46	arthralgia, wrists	2 days after Surgam® intake	2 weeks	III	no
2/*K	F/43	strain, ankle	2 days after Surgam® intake	4 weeks	IV	no
3/K	M/45	muscular pain, forearm	14 days	1 week	II	no
4/K	F/49	tendonitis, achilles	1 year	2 weeks	III	yes
5/K	M/17	tendonitis, achilles	3 weeks	2 weeks	III	yes
6/K	F/34	tendonitis, left leg	3 weeks (2 days after its end)	>2 weeks	II	yes
7/K	F/19	tendonitis, knee	1 day	4 weeks	III	yes
8/K	M/76	arthralgia, foot	1 day	>1 week	III	no
9/K	F/68	arthralgia, hands	1 year	1 week	III	no
10/P	F/53	tendonitis, hips	2 weeks (10 days after its end)	2 weeks	III	yes
11/K	F/37	arthritis, right hand	3 weeks	1 week	III	no
12/*P, K	M/35	superficial thrombophlebitis, leg	3 days	4 weeks	III	no

* Past-history of acute summer contact dermatitis with P (*P) or K (*K).

Table 3. Results of standard patch test series, patch tests (PT) and photopatch tests after irradiation by total spectrum (TS) and UVA (UVA) with the topical ointment and ketoprofen

Patient no.	European standard series	Ketoprofen 2.5% pet.			Ketoprofen 1% pet.			Patient's ointment		
		PT	TS	UVA	PT	TS	UVA	PT	TS	UVA
1	BP, FM, E	ND	ND	ND	—	++	+++	ND	ND	ND
2	BP	—	—	+++	—	—	+++	—	+++	+++
3	BP	ND	ND	ND	—	—	++	—	++	+++
4	ND	ND	ND	ND	+	ND	+++	++	ND	+++
5	FM	ND	ND	ND	—	++	++	++	+++	+++
6	Ni, C	ND	ND	ND	—	—	++	—	++	++
7	Ni	—	++	++	—	++	++	—	++	+++
8	BP	—	+	+	—	+	+	—	+	+
9	Ni, Co	—	+	+++	—	+	++	—	+	+
10	Ni	—	—	++	—	—	++	—	++	+++
11	FM	—	—	+	—	—	—	—	+	++
12	Ni, FM	ND	ND	ND	—	++	+++	—	++	+++

BP: balsam of Peru, FM: fragrance mix, C: colophony, E: epoxy resin glue, Ni: nickel sulfate, Co: cobalt chloride, ND: not done.

molecule were strongly positive (+++) (Fig. 2). In the 10 other patients with photocontact dermatitis, photopatch tests were positive with the patient's own ointment. The intensity of photopatch test response was higher after UVA irradiation than with total spectrum light. We also observed positive but weak reactions with non-irradiated patch tests in 2 cases (nos. 4 and 5). In patient no. 4, there was an edge-effect on the non-irradiated KP test area. None of our patients reacted to the components of the ointment base. In all cases, we obtained positive (+ to +++) photopatch tests with KP 2.5% pet. (6/6) and/or 1% pet. (11/12). There were no significant differences in the intensity of reaction observed, regarding to the 2 different concentrations of KP, except for patient no. 11. All 12 patients were tested to KP, TA, alminofen, flurbiprofen, ibuprofen and naproxen. Only 4 patients were tested to fenoprofen (cases nos. 9 to 12). We observed a reaction to both KP and TA in all cases (12/12), but patch and photopatch tests with the other APADs remained negative in all 12 patients.

Reactions to fenofibrate, oxybenzone, sulisobenzonone and unsubstituted benzophenone are listed in Table 4. We observed positive photopatch tests with fenofibrate in 8/12 cases. In 1 subject, there was a weakly positive (+) non-irradiated patch test. In 2 patients, there was a reaction after irradiation with total spectrum only. Photopatch tests were positive with oxybenzone in 3/12 cases, and with unsubstituted benzophenone in 11/12 cases, with photoaggravation in patient no. 2. Phototesting with sulisobenzonone was negative in all cases (0/12). All patch tests and photopatch tests in control subjects were negative.

Discussion

In each patient, we observed at least positive photopatch tests to KP, TA and another benzophenone-containing molecule. However, no positive reaction was observed with other APADs.

Both medical history and cutaneous examination



Fig. 2. Phototesting results in case no. 1. Photopatch tests show strongly positive (+++) reactions to tiaprofenic acid, ketoprofen, fenofibrate and unsubstituted benzophenone, 2 days after 10 J/cm² UVA irradiation.

in our 12 patients indicated allergic photocontact dermatitis, rather than phototoxicity. Photocontact dermatitis from TA observed in the first 2 patients is infrequent (3, 14, 20, 21). As TA is not available

in topical form in European countries (2), the past history and the results of phototesting in the first 2 patients strongly suggest that KP is the sensitizer. The 10 patients did not apply KP ointment on diseased or excoriated skin, which could be considered as a sensitization risk factor. The other clinical data were concordant with those previously reported, including the possibility of mild forms (7), the necessity for potent topical corticosteroids (12), and other sensitivities (2, 11) to chemicals often present in dressings or topicals, such as balsam of Peru, fragrance mix and colophony.

On the basis of our negative control patients, we excluded false-positive phototoxic reactions, using low concentrations of unsubstituted benzophenone and avoiding the use of fenofibrate extracted from a coating containing erythrosin (15). KP 1% pet. often seems as effective as 2.5% pet. in detecting photoallergic reactions. TA 1% pet. also appears to be more adequate (3, 13) than a higher concentration, which may provoke a phototoxic reaction (20, 21). The action spectra of photosensitizing APADs are often found in the UVA range (22), as supported by our *in vivo* observations that showed more intense reactions after irradiation with UVA alone. The 2 positive patch tests observed with fenofibrate after polychromatic irradiation only (cases nos. 2 and 5) argue for the role of UVB light. Indeed, the spectrum of fenofibrate seems to be in the UVB range, but may be converted *in vivo* to the UVA range (15). Irradiation with both UVA and UVB (or polychromatic) sources is therefore necessary to detect cross-sensitivity to other molecules, particularly fenofibrate.

Each patient had positive photopatch to both KP and TA. Despite analysis of the earlier literature, it was not possible to find a cross-reactivity pattern concerning APADs, particularly KP and

Table 4. Results of phototesting studying cross-reactions: patch tests (PT) and photopatch tests after UVA irradiation (UVA) and total spectrum (TS)

Patient no.	Ketoprofen			Tiaprofenic acid 1% pet.			Fenofibrate 10% pet.			Oxybenzone 10% pet.			Sulisobenzonone 10% pet.			Unsubstituted benzophenone 1% pet.		
	PT	TS	UVA	PT	TS	UVA	PT	TS	UVA	PT	TS	UVA	PT	TS	UVA	PT	TS	UVA
1	—	++	+++	+	+++	+++	—	+++	+++	—	—	—	—	—	—	—	+++	+++
2	—	—	+++	—	—	+++	—	+++	—	—	—	—	—	ND	—	++	ND	+++
3	—	—	++	—	—	++	—	—	—	—	—	—	—	—	—	—	+	—
4	+	ND	+++	—	ND	+++	—	ND	+	—	ND	+	—	ND	—	—	ND	+
5	—	++	++	—	++	++	—	+	—	—	—	—	—	—	—	—	++	++
6	—	—	++	—	—	++	—	—	—	—	—	—	—	—	—	—	—	++
7	—	++	++	—	++	++	+	+	++	—	—	—	—	—	—	—	++	++
8	—	+	+	—	—	+	—	—	—	—	—	—	—	—	—	—	+	—
9	—	+	+++	—	+	+	—	+	+	—	+	+	—	—	—	—	+	+
10	—	—	++	—	—	++	—	+	+	—	—	—	—	—	—	—	—	—
11	—	—	+	—	—	+	—	—	—	—	—	—	—	—	—	—	—	+
12	—	++	+++	—	++	++	—	+	++	—	—	+	—	—	—	—	++	++

ND: not done.

TA. Our results indicate cross-reactivity, because the 10 patients suffering from photocontact dermatitis had probably never been exposed to TA before. This cross-reactivity argues for a similar structure in both KP and TA being responsible for photoallergy to these molecules.

We observed no reaction to alminoprofen, fenoprofen, flurbiprofen, ibuprofen, or naproxen. This probably indicates that the arylpropionic acid structure, common to APADs, is not responsible for photoallergy to KP or TA. It has been assumed (23) that the antigenic determinant of the arylacanoic acids corresponded to the aryl structure, separated from the carboxyl group by at least one C atom (Fig. 1). No subsequent paper could systematically confirm this assumption, and it could not be verified in our patients. Moreover, some published cases reporting cross-sensitivity to several different APADs (Table 1) seem paradoxical, such as a positive photopatch test to KP and positive patch and photopatch tests to ibuprofen, but no reactions to ibuprofen or naproxen (7). Other authors (11) recently postulated that the sensitizing potential of APADs was due to the presence of an aldehyde group in the molecules. This was sustained by a high rate of sensitization to cinnamic aldehyde and by a comparison of chemical formulae. Although little is known about the cutaneous metabolism of APADs, this hypothesis seems weak. It remains unlikely in our cases, since we observed only 4 patients with a reaction to fragrance mix (which contain cinnamic aldehyde 1%). Likewise we have to consider that the patients who use topical APADs frequently make use of other available topical NSAIDs (12) and many fragrant and aromatic topical medicaments, which are traditionally employed to treat post-traumatic and rheumatic diseases. This probably results in co-sensitization rather than in cross-sensitization.

Fenofibrate elicited positive reactions in 8 patients. This is suggestive of the existence of cross-reactions to KP or TA, because of reaction to a substance to which the patients had not previously been exposed (patient no. 11 excepted). A benzophenone moiety was suspected as being the common structure responsible for cross-photosensitivity between KP and fenofibrate (4, 15).

Positive photopatch tests were observed to unsubstituted benzophenone in 11 of the 12 patients. Such frequent positive reactions clearly indicate the rôle played by this non-arylpropionic moiety of KP. This benzophenone structure is likewise structurally closely related to the thiophene-phenylketone part of TA (16). The lack of reaction to the unsubstituted benzophenone in the patient no. 10 does not exclude our hypothesis, since she reacted to KP, TA and fenofibrate. Concentrations

of unsubstituted benzophenone higher than 1% may perhaps be necessary in a few cases.

We observed only 3 patients with a positive reaction to oxybenzone, and none reacted to sulisobenzene. Substituted benzophenones, trade-marked Uvinuls, are different molecules absorbing UV light (24), and benzophenone-3 (oxybenzone), benzophenone-4 (sulisobenzene), benzophenone-8 (dioxibenzone) and benzophenone-10 (mexenone) are widely used in sunscreens and in cosmetics, such as "anti-aging" creams, hair sprays and shampoos (25, 26). As they may induce contact and photocontact dermatitis (25–27), it was postulated that they, and particularly oxybenzone, could induce occult sensitization to other benzophenone-containing molecules such as KP (4). As we detected only 3 positive reactions to oxybenzone in our patients, this presumption is probably rarely the case. Moreover, use of sunscreens was missing in most of our patients, even though oxybenzone may be included but not indicated in cosmetic formulations (25, 26). The absence of systematic cross-reactions between substituted benzophenones, such as oxybenzone, sulisobenzene or mexenone, was previously reported (25, 26, 28). Successive substitutions of side chains on a benzophenone structure affect its electronic volume and the steric accessibility of the molecule (29). Moreover, the oxygen atoms give rise to a relative excess of electrons, i.e., lower reactivity of the hapten with reactive protein residues. They also induce hydrogen bonds between ketone and hydroxyl functions of oxybenzone and sulisobenzene, thus modifying their steric conformation further. These facts are likely to influence the haptization reaction, and may be able to reduce or even suppress the sensitizing capacities of the molecule. This seems all the more likely in our patients, 8 of whom reacted to fenofibrate (1 side chain), only 3 to oxybenzone (2 side chains) and none to sulisobenzene (3 side chains), but still does not exclude that cross-reactions exist in some people sensitized to the benzophenone moiety.

However, in some cases of photoallergy to KP, as in our patients nos. 4, 5, the optimal drug penetration obtained by the gel formulation seems just as important as light for the development of contact allergy (8). They had positive patch tests with the ointment, which were worsened after UVA irradiation, even when positive tests with KP were

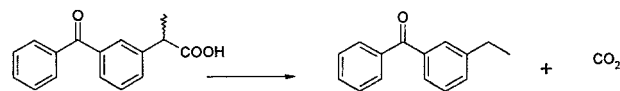


Fig. 3. Photodecarboxylation of ketoprofen. Photodegradation of ketoprofen leads to 3-ethylbenzophenone as a major photoproduct (according to 31).

obtained after UVA irradiation only. Exposure to UVA (or to UVB, according to the UV spectrum range of each molecule) provokes chemical non-enzymatic transformation of the hapten into a more excited reactive compound, which facilitates or enhances its fixation to its lymphocytic receptor (30). Some authors (31) recently demonstrated that, when irradiated in vitro, KP gave rise to several compounds involving benzophenone photochemistry, and especially 3-ethyl-benzophenone (Fig. 3). This major photodegradation product contains the benzophenone moiety but lacks the propionic acid side chain, and is probably responsible for the photoallergic reaction to KP. These data are consistent with our in vivo data, which indicate the absence of involvement of the arylpropionic acid function in photoallergy to KP or TA, and the subsequent absence of cross-sensitivity between KP or TA and APADs without the benzophenone or thiophene-phenylketone moiety.

Conclusion

Photoallergy to KP and TA involves the benzophenone moiety of KP or the closely related thiophene-phenylketone part of TA, rather than their arylpropionic acid function. Concomitant reactions sometimes observed with other APADs (not containing a benzophenone structure) result from co-sensitization rather than from cross-reactivity. The use of molecules containing a benzophenone (or a closely related) structure, like TA, fenofibrate and oxybenzone, should be avoided in patients who develop photoallergy or photoaggravation of contact dermatitis from KP. As a benzophenone mix (25) was suggested to detect sensitivity to benzophenones, we propose the inclusion of unsubstituted benzophenone (1% pet.) in standard phototesting, to detect photoallergy to benzophenone-containing or benzophenone-related molecules.

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