

Allergic and photoallergic contact dermatitis from ketoprofen: results of (photo) patch testing and follow-up of 42 patients*

VERLEE DEVLEESCHOUWER, RIK ROELANDTS, MARSAN GARMYN AND AN GOOSSENS

Department of Dermatology, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium

Background: Photoallergic contact dermatitis from topical ketoprofen (KP), a nonsteroidal anti-inflammatory agent, is a well-known side effect.

Objectives: To investigate photo-contact allergic reactions to KP and other nonsteroidal anti-inflammatory drugs (NSAIDs), sunscreens, and fragrance components as well as the presence of prolonged photosensitivity related to it.

Patients/Methods: From June 1993 to June 2007, 42 patients were patch tested and photopatch tested with the ingredients of a KP preparation and other relevant substances. A questionnaire was performed in order to determine the importance of prolonged photosensitivity; 40/42 did respond.

Results: 38 patients showed photo-contact reaction, 1 photoaggravated reaction, and 3 contact allergic (CA) reaction to KP. Simultaneous photo-contact allergic reactions were frequently observed not only to structurally related but also to non-structurally related NSAIDs and sunscreens. Simultaneous CA to fragrance components was common. 1/3 of the patients reported prolonged photosensitivity, i.e. from 1 up to 14 years after having stopped KP application.

Conclusions: The history is often not a good guidance to determine KP-related (photo) allergic contact dermatitis and the clinical symptoms severe, sometimes requiring hospitalization, and/or systemic corticosteroids. As for the association between KP and sunscreen intolerance (being 1 of the possible causal factors for recurrent dermatitis), routine standard photopatch testing with KP might be indicated.

Key words: allergic contact dermatitis; benzophenones; cross-reactions; etofenamate; fragrances; ketoprofen; nonsteroidal anti-inflammatory agents; octocrylene; photopatch test series; photosensitivity. © Blackwell Munksgaard, 2008.

Accepted for publication 19 September 2007

Ketoprofen [(KP); 2-(3-benzoylphenyl) propionic acid; Fig. 1], an arylpropionic acid derivative (APAD), belongs to the group of nonsteroidal anti-inflammatory drugs (NSAIDs). It is mostly used for musculoskeletal diseases because of its analgesic and anti-inflammatory effects. It was synthesized by Rhone-Poulenc SA (Antony, France) in the late 1960s (1) and sold internationally since 1973. Over the years, this drug came on the market in more than 70 different countries in

the form of systemic and topical preparations. The first cases of allergic dermatitis from the topical use of KP-containing products were reported by Italian dermatologists in 1983 (2, 3), and the first report on photoallergic contact dermatitis came from a Spanish dermatologist in 1985 (4). In the following 2 decades, cases of contact allergic (CA), photo contact allergy (PCA) and photo aggravated contact allergy (PACA) contact dermatitis were increasingly reported, first from the Mediterranean countries (2–4) and Japan (5) but later on, also from less sunny areas in northern Europe. As the use of topical KP (Fastum[®] gel; Menarini Benelux, Zaventem, Belgium) became

*Also in the name of the Belgian Contact & Environmental Dermatitis Group (BCEDG).

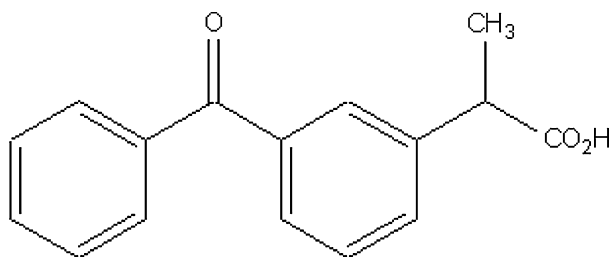


Fig. 1. Chemical structure of the ketoprofen molecule.

popular in Belgium in the 1990s, many patients have consulted dermatologists with mainly photocontact dermatitis, often with severe and extensive symptoms. Therefore, the Belgian Contact and Environmental Dermatitis Group (BCEDG) decided in 2001 to perform patch test (PT) and photopatch test (PPT) with Fastum gel, its constituents, and related materials in all patients suspected of dermatitis from it, the results of which were partly reported in 2004 (6). In the present article, we report on a series of 42 patients who were diagnosed with CA, PCA, or PACA from KP between 1993 and 2007 in our department.

Patients and Methods

Patients

During the period from June 1993 to June 2007, 42 Caucasian patients with a suspected (photo) allergic contact dermatitis from KP were investigated in our CA unit.

36 of 42 (photo) contact allergy tests took place between November 2000 and June 2007. Each patient was asked to give information about personal atopy status, history of polymorphic light eruption (PLE), the topical products used, recent history of sun exposure (as a trigger for the skin lesions), and delay time between first day of KP application and appearance of the skin eruption. We categorized the localization and the type of the skin lesions and evaluated the need for systemic treatment with corticosteroids, emergency visits, or subsequent hospitalization. By telephone and letters, a questionnaire was performed in all 42 patients in order to determine the presence of prolonged photosensitivity, the latter being defined as the appearance of a skin reaction or the recurrence of dermatitis in relation to sun exposure, after having stopped KP application. Of the 42 patients contacted, 40 did respond.

Besides the cases reported in this article, a few subjects (the exact number is not known) were seen at the outpatient clinic with dermatitis most likely induced by Fastum; however, they refused or did not show up for further testing.

PT and PPT

The PPTs were performed 1 month or more after complete resolution of the dermatitis. Almost all patients were patch tested with the European standard series (Hermal, Reinbeck, Germany). Other test substances for PT and PPT along with their test concentration and vehicle are listed in Table 1. All ingredients of Fastum gel were provided by Menarini Benelux: KP, *Lavandula* sp. (RC Rinaldi-Ceroni (Italy) [syn: oil of lavender (7)], *citrus aurantium dulcis* [syn: oil of orange flowers or neroli oil (7)], carbomer 940, and diethanolamine. Because in Belgium the popularity of both Fastum and Flexium[®] gels (Melisana, Brussels, Belgium) for over-the-counter (OTC) treatment of musculoskeletal complaints is comparable, we photopatch tested some components of the latter in many of our patients, i.e. the active principle etofenamate, *Eucalyptus* sp. [syn: oil of eucalyptus (7)], and *Pinus Sylvestris* [syn: oil of pine needles (7)]. Additional PPTs were carried out with NSAIDs, which included ibuprofen, naproxen and diclofenac, and sunscreens, which included the substituted benzophenone derivatives benzophenone-3 (syn: oxybenzone) and benzophenone-4 (syn: sulisobenzene). The exact number of patients patch tested and photopatch tested with all substances is given in Table 1.

The PTs were performed on 1 side of the patient's back (D0), using patch test chambers (Van der Bend, Brielle, The Netherlands) mounted on Micropore[™] (3M Health Care, Borken, Germany) and covered with Mefix[®] (Mölnlycke Health Care, Göteborg, Sweden). The PTs were removed and read at D2 and again at D4, according to International Contact Dermatitis Research Group recommendations. On the opposite site, the substances were similarly patch tested at D0 and irradiated (5 J/cm²) at D2 with ultraviolet (UV) A, using Philips Performance 100W-R lamps. Readings of the PPTs were performed after 2 days, sometimes later, except in 2 patients whose PPT were read 1 day after irradiation.

Results

The age of the 12 females and 30 males at the moment of testing ranged between 14 and 70 years and between 19 and 60 years, respectively. 11 patients (26%) had a history of personal atopy and 5 a known PLE; 4 more have been investigated for PLE but were negative.

All 42 patients had used topical KP: 41 Fastum gel with 1 of them also Kétum[®] gel (Menarini France, Rungis, France) and 1 only Profenid[®] gel (Sanofi-Aventis France, Paris, France), the

latter 2 preparations also containing KP and bought during a holiday in France. Some of them had also used other topical NSAIDs, i.e. 5 etofenamate (Flexium gel), 1 phenylbutazone (Butazolidin® ointment; Geigy, Basel, Switzerland), and another 1 diclofenac (Voltaren® Emulgel; Novartis CH, Vilvoorde, Belgium).

A recent history of sun exposure was present in 35, probable in 4, and absent in 3 patients. The delay time between the first day of application of KP and the start of the first skin eruption varied between 1 and 63 days (mean 15 days), the late onset always being related to sun exposure. The skin lesions were restricted to the site of application in 14 (33%) but disseminated in 28 patients (67%). The skin lesions were pruritic and papulovesicular in 42, bullous in 21 (Fig. 2), oedematous in 28, and erythema exudativum multiforme-like in 2 patients. Most of them presented with several types of skin lesions. 15 patients (36%) needed systemic treatment with corticosteroids. Emergency visits in the hospital occurred in 3 and hospitalization in 4 patients.

The questionnaire about prolonged photosensitivity was answered by 40 patients and gave the following results: after having stopped the application of KP, the skin reactions appeared for the first time or recurred in relation to sun exposure between 1 and 8 weeks in 12, between 25 and 52 weeks in 5, up to 2 years in 1, up to 3 years in 3, up to 4 years in 1, up to 5 years in 2, up to 6 years in 2, and even up to 14 years in 1. In total, 13 of 40 patients (30% or approximately one third) reported a prolonged photosensitivity up to 1 year or more.

Regarding the results of PT and PPT (Table 1), PPT with KP gave a positive reaction at the irradiated site in 38 patients, pointing to PCA, and in 1 both at the irradiated and non-irradiated site, pointing to PACA (PT aggravated with more than 1+ after irradiation with UVA). 3 patients presented with a nonconvincing history of sun exposure, so only PT were performed showing CA.



Fig. 2. Ketoprofen-induced vesiculo-bullous dermatitis.

In these cases, PACA cannot be totally excluded, however.

In the 20 patients who were simultaneously tested with oil of orange flowers 2% petrolatum (pet.) and 5% alcohol (alc.), the essential oils present in Fastum gel, 2 positive reactions were noticed to the latter only. In the patients who were tested with oil of orange flowers in only 1 concentration and vehicle, 0 of 1, 1 of 8, and 2 of 11 showed a reaction to 2% pet., 5% pet., and 5% alc., respectively. So, in 40 patients tested with oil of orange flowers, 5 positive reactions (12.5%) were observed in total. In the 21 patients who were simultaneously tested with oil of lavender 2% pet. and 5% alc., 2 positive reactions were noticed to the latter only. In patients who were tested with oil of lavender in only 1 concentration and vehicle, 2 of 10 and 1 of 9 patients showed a reaction to 2% pet., and 5% alc., respectively. So, in 40 patients tested with oil of lavender, 5 positive reactions (12.5%) were observed in total. 2 patients reacted to both oil of orange flowers and oil of lavender. No positive reactions were seen to carbomer 940 or diethanolamine, components of the excipient in Fastum gel.

With regard to etofenamate, the following reactions were observed: 4 CA, 15 PCA, and 5 PACA of a total of 36 patients tested. The possibility of PACA could not be excluded in 1 case because PPT was not performed. As to the essential oils in Flexium, 2 of 8 and 2 of 7 patients reacted positively to oil of eucalyptus 2% pet. and oil of pine needles 2% pet., respectively. 1 patient reacted positively to 3 essential oils, i.e. orange flowers (Fastum), eucalyptus, and pine needles (Flexium).

In a total of 36 patients, additional testing with ibuprofen and naproxen showed 1 CA and 2 PCA, respectively. Suprofen gave positive PPTs in 21 (91%) of 23 patients with PCA from KP. 1 patient was diagnosed with simultaneous CA to ibuprofen and PCA to naproxen, diclofenac, and fenoprofen.

Benzophenone-3 gave rise to 19 PCA and 2 PACA in a total of 33 PPT (61%). In the group of 13 patients reporting a prolonged photosensitivity of more than 1 year, 9 (75%) presented with PCA from benzophenone-3, 1 reacted negatively, but 3 had not been tested with this sunscreen. No positive PT or PPT reactions were seen to benzophenone-4, except for 1 doubtful reaction on PPT. Some other sunscreens also showed positive results on PPT: *t*-butylmethoxydibenzoylmethane (5 PPT and 1 PCA), mexenone (syn: benzophenone-10) (5 PPT, 1 PCA, and 1 doubtful PCA), isopropyl dibenzoylmethane (4 PPT and 4 PCA), and octocrylene (4 PPT and 3 PCA).

CA to fragrance mix (FM) was noted in 22 of 40 patients tested (52.5%). Several individual components tested positively and cinnamyl alcohol in particular, i.e. in 11 of 18 patients tested (61%) (Table 1). CA to *Myroxylon pereirae* (balsam of Peru) was noted in 18 of 39 patients tested (46%).

A recently performed questionnaire within the BCEDG showed 10 more cases of CA, 22 PCA, and 6 PACA to KP. Most reactions were accompanied by co- and/or cross-reactions with other NSAIDs and sunscreens, and some patients also suffered from prolonged photosensitivity. More-

over, as in our department, more subjects had reacted clinically to Fastum but had not been further investigated (the exact number is not known either).

Discussion

Photoallergic reactions are classical T-cell-mediated or delayed-type hypersensitivity reactions of the skin in response to a photoallergen (or a cross-reacting chemical) to which a subject was sensitized in the past (8). Skin changes resemble those of CA dermatitis and may expand beyond the site

Table 1. Results of patch tests and photopatch tests after irradiation with ultraviolet A*

Allergen	Number of patients tested (PT)	Number of patients tested (PPT)	CA	PCA	PACA
Fastum gel (2.5% KP)	23	13	4	7	3
KP 1% pet.	28	27	1	26	1
KP 2% pet. (6)	5	5	0	5	0
KP 5% pet.	10	8	2	8	0
Etofenamate 2% pet.	36	35	4	15	5
Oil of orange flowers 2% pet.	21	20	0	0	0
Oil of orange flowers 5% pet.	8	3	1	0	0
Oil of orange flowers 5% alc.	31	29	4	0	0
Oil of lavender 2% pet.	31	24	2	0	0
Oil of lavender 5% alc.	30	28	3	0	0
Oil of eucalyptus 2% pet.	8	1	2	0	0
Oil of pine needles 2% pet.	7	1	2	0	0
Carbomer 940 10% aqua	24	21	0	0	0
Diethanolamine 1% pet.	32	30	0	0	0
Ibuprofen 2% pet.	36	36	1	0	0
Naproxen 2% pet.	36	36	0	2	0
Diclofenac 5% pet.	34	34	1	1	0
Alclofenac 2% pet.	19	19	0	3	0
Suprofen 5% pet.	23	23	0	21	0
Pranoprofen 5% pet.	7	7	0	0	0
Fenoprofen 2% pet.	9	9	0	1	0
Piroxicam 1% pet.	5	5	0	0	0
Tenoxicam 1% pet.	4	4	0	0	0
Indomethacin 2% pet.	4	4	0	0	0
Niflumic acid 5% pet.	5	4	1	0	0
Probenecid 2% pet.	2	2	0	0	0
Benzophenone-3 10% pet.	34	33	0	19	2
Benzophenone-4 5% pet.	23	23	0	1?	0
<i>t</i> -butylmethoxydibenzoylmethane 5% pet.	6	5	0	1	0
Ethylhexylmethoxycinnamate 2% pet.	5	5	0	0	0
Phenylbenzimidazol sulfonic acid 5% pet.	5	5	0	0	0
Mexenone 10% pet.	5	5	0	1+ (1?)	0
Isopropylidibenzoylmethane 2% pet.	4	4	0	4	0
Octocrylene 10% pet.	5	4	0	3	0
Fragrance mix 8% pet.	40	NT	22	0	0
Amylcinnamal 1% pet.	18	NT	1	0	0
Cinnamal 1% pet.	18	NT	0	0	0
Cinnamyl alcohol 1% pet.	18	NT	11	0	0
<i>Evernia prunastri</i> (oak moss) 1% pet.	18	NT	6	0	0
Isoeugenol 1% pet.	18	NT	1	0	0
Eugenol 1% pet.	18	NT	4	0	0
Hydroxycitronellal 1% pet.	18	NT	1	0	0
Geraniol 1% pet.	18	NT	0	0	0
<i>Myroxylon pereirae</i> (balsom of Peru) 25% pet.	39	NT	18	0	0

CA, contact allergy; KP, ketoprofen; NT, not tested; PACA, photoaggravated contact allergy; PCA, photo contact allergy;

PPT, photopatch test; PT, patch test; ?, doubtful reaction.

*Entries in bold are 'KP series' tested in our department since 2001.

of topical application. The clinical presentation should not be mistaken for erysipelas because both diseases can present with erythema, oedema, and bullae. Several patients had been indeed diagnosed as such and had received systemic treatment with antibiotics prior to the diagnosis of photoallergic contact dermatitis.

Sunscreens (mainly benzophenones and dibenzoylmethane derivatives) are the most common agents giving rise to photoallergic contact dermatitis (8); but in recent years, increasing numbers of photoallergic reactions because of NSAIDs, mainly KP (9), are reported. The problem occurs in those countries where KP has been commercialized and frequently used (e.g. in 2006, 451 278 units of Fastum gel have been sold in Belgium). However, it might also give problems in other parts of the world (such as the UK), where it seems to be infrequently used and adverse reactions only rarely seen (I. R. White, St. John's Institute of Dermatology and St. Thomas' Hospital, London; J. Ferguson, Ninewells Hospital, Dundee). Indeed, people are travelling and are thus exposed to popular products marketed in other parts of the world. This was illustrated by the use by 2 of our patients of KP-containing Profenid and Kétum gels commercialized in France. In most recent years, Spanish authors (10, 11) did report PCA to the pharmacologically active (S)-(+)-enantiomer (dex-ketoprofen) of the racemic mixture of KP (12). They consider that, as with KP, similar problems of PCA are likely to be expected in the following years because it is now on the market as a topical preparation in several Mediterranean countries.

As observed by other authors (5, 6, 9, 13, 14), the severe dermatitis experienced by 42 patients after the use of topical KP was attributable to PCA (38 subjects), PACA (1 subject), and CA (3 subjects) from KP, although in the latter, the lack of PPT does not exclude the possibility of PACA. In our series of PPT, the possibility of phototoxic reactions cannot be fully excluded but the symptoms and the follow-up regarding prolonged photosensitivity make this less probable. Moreover, several authors did argue against the phototoxic nature of these reactions: Le Coz et al. (15) performed PPT with KP 1% pet. in 15 control subjects and none of them reacted positively; similar results were found in the study of Sugiura et al. (16), where PPT was carried out in 335 patients, of whom only 1 showed a positive reaction. Moreover, applying 10% KP on guinea-pigs showed no phototoxic reactions, whereas it induced photoallergic reactions at all dosages (0.5–2%) (17).

Until the end of 2000, KP was tested in our department at a concentration of 5% pet.

Because of severe PPT reactions, however, in 2001, the concentration was lowered to 2% and later to 1%, which is equally adequate to diagnose (photo) contact allergy (15). As for most of the photoallergens, the action spectrum of KP lies mainly in the UVA range (18), hence the irradiation with 5 J/cm² UVA. Some articles (15, 19, 20) did report that UVB may also intervene, suggesting that the total spectrum irradiation of the PPT may show photoallergies that are not found with UVA alone. Keeping this in mind, it is possible that, also in this study, the problem of photoallergic contact dermatitis from KP is still underestimated.

Concerning the molecular basis of PCA from KP, many authors (15, 17, 20–22) point out the benzophenone moiety (double benzene rings linked by a ketone group; Fig. 1) as the cause, which also explains possible cross-reactions with benzophenone-derived chemicals, i.e. benzophenone-3 (19 PCA and 2 PACA of 33 tested), suprofen (21 PCA of 23 tested), tiaprofenic acid, fenofibrate, and amiodarone. The arylpropionic function, causing the anti-inflammatory effect, does not seem to interfere in the mechanism of photoallergy to KP (15, 20). Indeed, when irradiated with sunlight, KP is photodecarboxylated leading to 3-ethyl-benzophenone (lacking the propionic acid side chain) as a major photoproduct (15). The absence of PCA to benzophenone-4 is, in agreement with the results of the other authors (15, 20), possibly explainable by the presence of a steric-encumbered ketone function (20).

Surprising though is the result of 3 PCA in 5 PPT for octocrylene, which is a more recently introduced sunscreen. Similar observations were made by Delplace and Blondeel, who reported in 2006 the first 3 cases of PCA to octocrylene (23). Hence, our results indicate that patients suspected of photo-contact allergy or positive PPTs to sunscreens should also be tested for photo-contact allergy to KP, being a possible cause of subsequent photo-contact allergic reactions to sunscreens, to benzophenone-3 in particular, but maybe also to not chemically related sunscreens. The opposite possibility, that the frequent use of benzophenone-3 in cosmetics can cause a subsequent PCA to KP, was already postulated by Horn et al. (24), giving the same testing advice.

PCA, PACA, or CA to etofenamate, an anthranilic acid derivative (AAD), being the active principle of Flexium gel, was observed in 24 of 36 patients tested. Until recently, (photo) contact sensitivity to etofenamate has been rarely reported (25) but this is perhaps underestimated. It is unclear why, in our test series, many patients suffer from simultaneous PCA from KP and

etofenamate as they belong to different groups of NSAIDs (AADs versus APADs). Associated photoallergic reactions between KP and other molecules without a benzophenone moiety, such as fentichlor, tetrachlorosalicylanilide, triclosan, tribromsalan, and bithionol, have been reported in the literature though (1). This might be because of a hyper-photosusceptibility to non-relevant allergens induced by photosensitivity to KP (1) or because of co-sensitization instead of cross-sensitization (15); patients who frequently use topical APADs also make use of other available topical NSAIDs. However, the majority of our patients did not remember having used Flexium or did not even know it.

In agreement with other authors (6, 20, 26, 27), co-sensitization is perhaps also a possible explanation for the common appearance of CA to FM and *M. pereirae* (balsam of Peru). Some of them (6, 20) considered a possible cross-sensitization between 'an aldehyde function' in the KP molecule and cinnamic aldehyde, a FM component. In our patients, however, reactions were most often seen to cinnamic alcohol (11 of 18 patients tested), whereas only 1 positive test was observed to amylcinnamal and none to cinnamal! This is in agreement with the observations of Girardin et al. (28), who remarked that there is no true aldehyde function in the KP molecule but suggested that cutaneous reactivity to cinnamic derivatives might represent a risk factor for KP sensitization.

With regard to the essential oils present in Fastum, the test conditions seem to be important because both oils of orange flowers and lavender gave more positive results when tested 5% in alc. instead of 2% or 5% in pet. This is the reason why it was decided, in May 2005, to continue testing only with the 5% alc. dilution. CA to them seems to be rare though (13) because each did react in only 12.5% of the patients. Except for 1, all presented with simultaneous reactions to FM and balsam of Peru, which could point to a cross-allergy with certain ingredients present in the essential oils, themselves being false negative. In our series, 6 patients with CA to FM and/or balsam of Peru have not been tested with oil of orange flowers or oil of lavender 5% in alc.

From the clinical point of view, our test series show a surprisingly high prevalence and duration of prolonged photosensitivity to KP. In most patients, this was present for a short period of time but also longer recurrences of photoallergic contact dermatitis were observed, even up to 14 years after having stopped the application of Fastum gel. The subsequent dermatitis was in all cases less severe than the original symptoms but mostly

expanding beyond the original application site. Cases of prolonged photosensitivity were already reported (20, 24, 29–31), but never of this magnitude or duration, although a prospective survey over a longer period of time has never been conducted before. A history of PLE was absent in all our patients who reported prolonged photosensitivity. The pathophysiological hypotheses are the following: (i) retention of the photoallergenic molecule in the skin, reported up to at least 17 days (5, 17), which can, however, not explain the long time intervals after having stopped the application; (ii) relapses induced by KP-contaminated objects such as bandages, clothing, trousers, and shoes (32), even after repeated washing; (iii) contact with relatives using topical KP, i.e. 'connubial' or 'consort' dermatitis (33); and (iv) last but not least, persisting contacts with molecules that are structurally related to KP or co-react on PPT.

In our testing series, it is remarkable that 12 of 13 patients reporting a prolonged photosensitivity of more than 1 year did react to benzophenone-3, which might have contributed to this condition. Indeed, in recent years, UV filters like benzophenone-3 and -4 are widely incorporated in commonly used cosmetics, such as lip balm (34), skin moisturizers, facial make-up, and 'anti-ageing' creams, in order to protect the skin against UV light exposure and to reduce photoageing of the skin (35). Moreover, they are also often incorporated in personal hygiene products, such as aftershaves, shower and bath gels, hair sprays, shampoos, and conditioners (36), in order to retard the photodegradation of the formulation (35). Hence, contact with such products may be relevant for recurrent photoallergic reactions as well.

Conclusion

In agreement with the literature, photoallergic contact dermatitis from KP is a common problem in our patient series, causing severe but also persistent dermatitis in many cases. A similar long follow-up and PPT results obtained in such a large series of patients have not been published before. We even did not take into account the patients suspected of intolerance to KP and who were not further investigated. As KP represents the majority of the cases of photoallergic reactions because of NSAIDs, the question arises whether the clinical benefit outweighs the disadvantages (9). Hence, serious measures are required for (OTC) use of topical KP and explicit warnings on sun exposure and prolonged photosensitivity should be given.

It might also be necessary to consider inclusion of KP routinely in a standard PPT series as the

diagnosis may be easily missed from the history (skin reactions may appear long after having stopped its application, and the patients do often not remember or mention having applied it). Last but not least, cross- or co-reactions between KP and sunscreens should be further investigated in order to provide better advice to allergic patients regarding the use of 'safer' cosmetics in the future and thus to prevent recurrences of photo-contact dermatitis from this source.

Acknowledgements

We thank Menarini and Melisana for providing us with the individual ingredients of their products, Fastum and Flexium, respectively. We also thank the 'Algemene Pharmaceutische Bond (APB Belgium)' for providing us with the sales numbers of topical NSAIDs in Belgium in 2006. We are also grateful to the members of the BCEDG, who provided us with their recent observations on KP (photo) contact allergy: A. Blondeel (University of Brussels, Université Libre de Bruxelles), B. Dezfoulan (University of Liège), C. Dierckxsens (University of Brussels, Vrije Universiteit Brussel), S. Kerre and N. Lateur (University of Brussels, ULB), L. Matthieu (University of Antwerp), L. Meuleman and A. Stockman (University of Ghent), and D. Tennstedt (University of Brussels, Université Catholique de Louvain).

References

1. Durbize E, Vigan M, Puzenat E et al. Spectrum of cross-photosensitization in 18 consecutive patients with contact photoallergy to ketoprofen: associated photoallergies to non-benzophenone-containing molecules. *Contact Dermatitis* 2003; 48: 144–149.
2. Valsecchi R, Falgheri G, Cainelli T. Contact dermatitis from ketoprofen. *Contact Dermatitis* 1983; 9: 163–164.
3. Angelini G, Vena G A. Contact allergy to ketoprofen. *Contact Dermatitis* 1983; 9: 234.
4. Alomar A. Ketoprofen photodermatitis. *Contact Dermatitis* 1985; 12: 112–113.
5. Sugiura M, Hayakawa R, Kato Y, Sugiura K, Ueda H. 4 cases of photocontact dermatitis due to ketoprofen. *Contact Dermatitis* 2000; 43: 16–19.
6. Matthieu L, Meuleman L, Van Hecke E, Blondeel A, Dezfoulan B, Constandt L, Goossens A. Contact and photocontact allergy to ketoprofen. The Belgian experience. *Contact Dermatitis* 2004; 50: 238–241.
7. O'Neil M J, Heckelman P E, Koch C B, Roman K J, Kenny C, D'Areca M J. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 14th edition. Whitehouse Station, Merck & Co Inc, 2006.
8. Goossens A. Photoallergic contact dermatitis. *Photodermatol Photoimmunol Photomed* 2004; 20: 121–125.
9. Dias R L, Gardeazabal J, Manrique P, Raton J A, Urrutia I, Rodriguez-sasiain J M, Aguirre C. Greater allergenicity of ketoprofen in contact dermatitis confirmed by use. *Contact Dermatitis* 2006; 54: 239–243.
10. Goday-Bujan J J, Rodriguez-Lozano J, Martinez-Gonzalez M C, Fonseca E. Photoallergic contact dermatitis from dexketoprofen: study of 6 cases. *Contact Dermatitis* 2006; 55: 59–61.
11. Gonzalez-Perez R, Trebol I, Garcia-Rios I, Arregui M A, Soloeta-Arechavala R. Photocontact dermatitis due to dexketoprofen. Report of 2 cases. *Actas Dermosifiliogr* 2006; 97: 456–459.
12. Barbanoj M J, Antonijoan R M, Gich I. Clinical pharmacokinetics of dexketoprofen. *Clin Pharmacokinet* 2001; 40: 245–262.
13. Hindsen M, Zimerson E, Bruze M. Photoallergic contact dermatitis from ketoprofen in southern Sweden. *Contact Dermatitis* 2006; 54: 150–157.
14. Sugiyama M, Nakada T, Hosaka H, Sueki H, Iijima M. Photocontact dermatitis to ketoprofen. *Am J Contact Dermat* 2001; 12: 180–181.
15. Le Coz C J, Bottlaender A, Scrivener J-N, Santinelli F, Cribier B J, Heid E, Grosshans E M. Photocontact dermatitis from ketoprofen and tiaprofenic acid: cross-reactivity study in 12 consecutive patients. *Contact Dermatitis* 1998; 38: 245–252.
16. Sugiura M, Hayakawa R, Suzuki M. A case of photocontact dermatitis due to ketoprofen. *Environ Dermatol (Nagoya)* 1996; 3: 370–377.
17. Nakazawa T, Shimo T, 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: 442–448.
18. Becker L, Eberlein-König B, Przybilla B. Phototoxicity of non-steroidal anti-inflammatory drugs: in vitro studies with visible light. *Acta Derm Venereol* 1996; 76: 337–340.
19. Leonard F, Adamski H, Bonneville A et al. Etude prospective multicentrique 1991-2001 de la batterie standard des photopatch-tests de la Société Française de Photodermatologie. *Ann Dermatol Venereol* 2005; 132: 313–320.
20. Durieu C, Marguery M-C, Giordano-Labadie F, Journe F, Loche F, Bazex J. Allergies de contact photoaggravées et photoallergies de contact au ketoprofène: 19 cas. *Ann Dermatol Venereol* 2001; 128: 1020–1024.
21. Bosca F, Miranda M A. Photosensitizing drugs containing the benzophenone chromophore. *J Photochem Photobiol B: Biol* 1998; 43: 1–26.
22. Bosca F, Miranda M A, Carganico G, Mauleon D. Photochemical and photobiological properties of ketoprofen associated with the benzophenone chromophore. *Photochem Photobiol* 1994; 60: 96–101.
23. Delplace D, Blondeel A. Octocrylene: really non-allergenic? *Contact Dermatitis* 2006; 54: 295.
24. Horn H M, Humphreys F, Aldridge R D. Contact dermatitis and prolonged photosensitivity induced by ketoprofen and associated with sensitivity to benzophenone-3. *Contact Dermatitis* 1998; 38: 353–354.
25. Chu C-Y, Chen Y-L, Lin L-J, Sun C-C. Allergic contact dermatitis from etofenamate without cross-sensitization to other anthranilic acid derivatives. *Dermatology* 2003; 206: 341–342.
26. 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 Dermat* 1996; 7: 220–223.
27. Hindsen M, Zimerson E, Garnemark V, Bruze M. Contact allergy in patients with photocontact allergy to ketoprofen. *Exog Dermatol* 2004; 3: 180 (Specific allergens).
28. 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.
29. Offidani A-M, Cellini A, Amerio P, Simonetti O, Bossi G. A case of persistent light reaction phenomenon to ketoprofen? *Eur J Dermatol* 2000; 10: 153–154.
30. Le Coz C J, El Aboubi S, Lefebvre C, Heid E, Grosshans E. Photoallergy from topical ketoprofen: a clinical, allergological and photobiological study (Poster). *Contact Dermatitis* 2000; 42: 47.
31. Albes B, Marguery M C, Schwarze H P, Journe F, Loche F, Bazex J. Prolonged photosensitivity following

- contact photoallergy to ketoprofen. *Dermatology* 2000; 201: 171–174.
32. Hindsen M, Isaksson M, Persson L, Zimersson E, Bruze M. Photoallergic contact dermatitis from ketoprofen induced by drug-contaminated personal objects. *J Am Acad Dermatol* 2004; 50: 215–219.
33. Mirande-Romero A, Gonzalez-Lopez A, Esquivias J I, Bajo C, Garcia-Munoz M. Ketoprofen-induced connubial photo-dermatitis. *Contact Dermatitis* 1997; 37: 242.
34. Veysey E C, Orton D I. Photoallergic contact cheilitis due to oxybenzone found in a lip cosmetic. *Contact Dermatitis* 2006; 55: 54.
35. Hughes T M, Stone N M. Benzophenone 4: an emerging allergen in cosmetics and toiletries? *Contact Dermatitis* 2007; 56: 153–156.
36. Alanko K, Jolanki R, Estlander T, Kanerva L. Occupational allergic contact dermatitis from benzophenone-4 in hair care products. *Contact Dermatitis* 2001; 44: 188–189.

Address:

A. Goossens
Department of Dermatology
University Hospital K.U. Leuven
Kapucijnenvoer 33
B-3000 Leuven
Belgium
Tel: +00 32 16 33 78 60
Fax: +00 32 16 33 70 12
e-mail: an.goossens@uz.kuleuven.ac.be