

Contact and photocontact allergy to ketoprofen. The Belgian experience

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Topical ketoprofen (KP) is widely used because of its anti-inflammatory effect. However, photocontact dermatitis is a side-effect. Between May 2001 and June 2002, the Belgian Contact & Environmental Dermatitis Group conducted a prospective, open patch and photopatch test study in 20 patients suspected of KP dermatitis. Severe skin symptoms requiring systemic corticotherapy occurred in 47%. 5 patients were hospitalized. 1 patient showed prolonged photosensitivity. All patients were tested with KP and the other constituents of KP gel. Attribution to KP was demonstrated in all cases. Patch and photopatch tests with KP 2% in petrolatum showed contact photoallergy in 17 patients, contact allergy in 1 patient and photoaggravated contact allergy in 2 patients. 5 patients also reacted to the fragrance components lavender (*Lavandula augustifolia*) oil and/or neroli (*Citrus aurantium dulcis*) oil 5% in alcohol. However, in 4 of these, irritant reactions to the ethanolic dilutions could not be ruled out. Additional tests with 3 non-steroidal anti-inflammatory drugs without benzophenone structure ibuprofen, naproxen and diclofenac identified only 1 contact allergic reaction to diclofenac. Cross-reactivity to the substituted benzophenones, oxybenzone and sulisobenzene occurred only to the first in less than 30% of the patients. A high frequency (69%) of contact allergy to fragrance mix was found. Dermatologists should be aware of the severity of photoallergic reactions to KP and the risk of cross-sensitization.

Key words: cross-reactivity; fragrance components; ketoprofen, medicaments; non-steroidal anti-inflammatory drugs, photopatch tests; photosensitivity. © Blackwell Munksgaard, 2004.

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Ketoprofen (KP) is a non-steroidal anti-inflammatory drug (NSAID) belonging to the arylpropionic acid derivatives (APADs). Topical KP is used in more than 70 countries because of its local analgesic and anti-inflammatory effects and low toxicity. However, since 1983, an increasing number of case reports of allergic and photoallergic contact dermatitis from KP have been published, first from the Mediterranean countries and later also from more northern European areas and from Japan (1–3).

As the use of topical KP (Fastum[®] gel, Menarini Benelux, Zaventem, Belgium) became very popular in Belgium, dermatologists were confronted with an increasing number of patients with mainly photocontact dermatitis. Skin symptoms were often severe and of long duration. Prolonged photosensitivity was seen in some cases. Therefore, the Belgian Contact & Environmental Dermatitis Group (BCEDG) decided in 2001 to perform patch and photopatch tests with Fastum[®] gel and its constituents in all patients suspected of dermatitis from it.

Patients and Methods

Patients

Between May 2001 and June 2002 20 Caucasian patients, 16 women and 4 men, aged 18–70 years (mean 42 years) were investigated by the participating BCEDG members.

There was a history of sun exposure in 17 patients. In 1 patient, skin symptoms started after using etofenamate gel (Flexium[®], Aventis Pharma, Brussels, Belgium) but there had been exposure to Fastum[®] gel as well.

A pruritic papulovesicular dermatitis was observed in 10 patients. Bullous lesions occurred in 6 patients. 2 patients showed marked oedema mimicking erysipelas. In 1 patient erythema multiforme-like lesions were noted. The eruption was localized to the site of application in 8 patients. Dissemination occurred in 11 patients. 9 patients required treatment with systemic corticosteroids, and 5 were hospitalized. Prolonged photosensitivity (4 months) was noted in 1 patient.

Patch and photopatch tests

The patients were tested at least 1 month after complete resolution of their dermatitis. 13 patients were patch tested with the Belgian standard series. Photopatch tests were performed in duplicate with Fastum[®] gel (16 patients) and its constituents (20 patients) kindly provided by Menarini Benelux, Zaventem, Belgium. They included KP 2% and 5% in white petrolatum (pet.), neroli (*Citrus aurantium dulcis*) oil 2% pet. and 5% in alcohol, lavender (*Lavandula augustifolia*) oil 2% pet. and 5% alc., diethanolamine 1% pet. and carbomer 940 10% in aqua. Additional photopatch tests were carried out with the APADs ibuprofen 2% pet. (18 patients) and naproxen 2% pet. (17 patients) and with the arylacetic acid derivative diclofenac 5% pet. (6 patients) and 2% pet. (2 patients). The benzophenone derivatives, 2-hydroxy-4-methoxybenzophenone (oxybenzone, benzophenone-3) 10% pet., and 2-hydroxy-4-methoxybenzophenone-5-sulphonic acid (sulisobenzone, benzophenone-4), 10% pet. (Chemotechnique Diagnostics AB), were photopatch tested in 15 and 12 patients, respectively. One set of tests was removed after 1 day and irradiated with 5 J/cm² of ultraviolet A (UVA). Test reactions were read at 1 and 3 days after irradiation. Positive reactions were graded + to +++ according to the International Contact Dermatitis Research Group recommendations (4).

Results

Table 1 shows the patch and photopatch test results of our series. Of the 16 patients tested with Fastum[®] gel, 11 had a contact photoallergy (CPA), 1 patient had a contact allergy (CA) and 4

a photoaggravated contact allergy (PACA). Photopatch testing with KP demonstrated CPA in 17/20 patients, CA in 1 patient and PACA in 2 patients. Strong positive (++ and +++) reactions were observed in all but 1 patient with no differences regarding the 2 test concentrations of KP.

5 patients showed positive (+ and ++) reactions to the fragrance components of the gel base. Lavender oil 5% alc. caused CPA in 3 patients and CA in 1, whereas neroli oil 5% alc. caused CPA in 1 patient, CA in 1 and PACA in another patient. In 3/5 patients, component reactions were less pronounced than ketoprofen reactions. To the other gel base components no clear positive reactions were observed.

Patch and photopatch tests with ibuprofen and naproxen remained negative in all tested patients. In one of the 8 tested patients, a CA to diclofenac was found. Photopatch tests with benzophenone-3 were positive in 4/15 patients. Benzophenone-4 remained negative in 12 tested patients. We found 9 positive patch test reactions to fragrance mix and 7 to balsam of Peru (*Myroxylon pereirae* resin) in 13 patients tested with the Belgian standard series.

Discussion

Our results demonstrate attribution to KP in all 20 cases of Fastum[®] gel allergy and contribute to the increasing reports of CPA and PACA to this NSAID. Although we tested only 2 control subjects who did not show any reaction to the photopatch tests with ketoprofen, the possibility of phototoxicity cannot be completely ruled out. However, the patients' symptoms, the lack of difference in test reactions to both 2% and 5%

Table 1. Results of patch (PT) and photopatch tests (PPT) after irradiation with ultraviolet A

Allergen	Number of patients	Positive PPT	Positive PT
Fastum [®] gel	16	16 (11 CPA)	5 (1 CA and 4 PACA)
Ketoprofen 2% pet.	20	20 (17 CPA)	3 (1 CA and 2 PACA)
Ketoprofen 5% pet.	18	18 (16 CPA)	2 (1 CA and 1 PACA)
Lavender oil 5% alc.	17	3 (3 CPA)	1 (1 CA)
Lavender oil 2% pet.	20	1	1
Neroli oil 5% alc.	17	3 (1 CPA)	2 (1 CA and 1 PACA)
Neroli oil 2% pet.	20	1	0
Diethanolamine 1% pet.	20	0	0
Carbomer 10% aq.	20	0	0
Ibuprofen 2% pet.	18	0	0
Naproxen 2% pet.	17	0	0
Diclofenac 5%, 2% pet.	8	1	1 (1 CA)
Benzophenone-3 10% pet.	15	4 (4 CPA)	0
Benzophenone-4 10% pet.	12	0	0
Fragrance mix 8% pet.	13	NT	9
Balsam of Peru 25% pet.	13	NT	7

CA, contact allergy; CPA, contact photoallergy; NT, non-tested; PACA, photoaggravated contact allergy.



Fig. 1. Bullous contact photoallergic dermatitis of lower leg.

KP and the occurrence of PACA in 4 patients point to allergic photocontact dermatitis rather than phototoxicity. In one report (5), patch and photopatch test series were performed in 12 patients with a history of photocontact dermatitis induced by KP (10 pat.) or tiaprofenic acid (2 pat.), and also in 15 control subjects: none of the controls showed positive reactions, indicating the photoallergic nature of KP reactions.

The action spectrum of KP is known to be predominant in the UVA range (5, 6). Severe and atypical clinical symptoms were present in 47% of our patients and dissemination of the eruption occurred in more than half (58%). Systemic



Fig. 2. Positive ultraviolet A-photopatch test to ketoprofen 2% and 5% pet.

corticotherapy was required in 47% and hospitalization in 26%.

Prolonged photosensitivity without re-exposure to KP has been described (6, 7) and was observed in 1 of our cases. 5 patients also demonstrated CPA, PACA and CA to lavender oil and/or neroli oil 5% in alcohol. The relevance of these findings is not clear. In 4 patients, irritant reactions to the ethanolic dilutions could not be completely ruled out because both substances remained negative when tested at 2% pet. Co-sensitization is another possibility, as lavender and neroli oil are known contact and photocontact allergens. Cross-reactivity between KP and tiaprofenic acid, fenofibrate and benzophenones is well known and involves the benzophenone moiety of KP (5). No reactions were found to the APAD's ibuprofen and naproxen without benzophenone structure. One patient showed a positive patch test to the arylacetic acid NSAID diclofenac. We consider this as a co-sensitization.

Cross-photosensitivity between KP and unsubstituted benzophenone is common but less frequently seen with substituted benzophenones. As in other series (5, 6), less than 30% of the patients showed positive photopatch tests to benzophenone-3 and none to benzophenone-4. This is thought to be due to successive substitutions of side chains on the benzophenone structure (5).

69% of our patients were contact allergic to fragrance mix. In 2 case-series (6, 8), 68% and 83% of the KP-allergic patients showed CA or PCA to fragrance mix, which is comparable to our findings. A possible explanation for this phenomenon could be the presence of an aldehyde function in KP and cinnamic aldehyde, a component of fragrance mix and balsam of Peru.

Conclusion

The Belgian experience underlines the warnings of other authors to avoid prescription of topical KP during sunny periods on exposed skin, in view of the risks of severe clinical symptoms, prolonged photosensitivity and cross-sensitizations.

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