

# Photoallergic contact dermatitis from ketoprofen in southern Sweden

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The non-steroidal anti-inflammatory drug ketoprofen is widely used for topical treatment. In Sweden, ketoprofen has been available for topical application since 1995. Photoallergic contact dermatitis from ketoprofen-containing topical preparations usually includes severe eczematous reactions. Ketoprofen is derived from propionic acid, and it is also a substituted benzophenone and therefore structurally similar to fenofibrate and sunscreen agents based on benzophenones. During the last 2 years, 35 patients have been referred to our department with suspected photoallergic or allergic reactions after having used ketoprofen-containing gels. Photopatch testing with the photopatch standard series, the ketoprofen-containing gels and their ingredients, fenofibrate, benzophenone-3, benzophenone-10 and benzophenone-4, was performed. Photoallergic reactions to ketoprofen were noted in 35 patients and a simultaneous contact allergy to ketoprofen in 2 patients. Simultaneous photoallergy to fentichlor, tetrachlorosalicylanilide and fenofibrate was registered in 74%, 40% and 73% of the patients, respectively.

**Key words:** benzophenone; fenofibrate; ketoprofen; photoallergic contact dermatitis; sunscreen; topical treatment. Journal compilation © 2006 Blackwell Munksgaard.

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Ketoprofen is a non-steroidal anti-inflammatory drug, a propionic acid derivative and at the same time a substituted benzophenone. In Sweden, ketoprofen is currently used orally, rectally and topically. It was introduced in Sweden for topical use in 1995 and since more than 3 years the topical treatment is available without prescription. The use of topical treatment of ketoprofen is increasing in Sweden (C. Luthman, personal communication), where 3 gels each containing 2.5% ketoprofen are available. Among propionic acid derivatives, ketoprofen is the one that frequently causes photoallergic contact dermatitis (1–6).

Photocontact allergy to ketoprofen has been reported since almost 20 years, mostly from the Mediterranean countries and Japan (1–6) but recently also from Belgium (7). In this study, we report on the results of photopatch testing 35 patients with a suspected photoallergic contact dermatitis from the use of ketoprofen-containing gels.

## Materials and Methods

### Patients

During the last 2 years, 35 patients have been referred to our clinic for further investigation

because of spreading eczematous reactions sometimes requiring treatment with internal corticosteroids after the use of ketoprofen-containing gels. A thrombosis was suspected in 2 of the patients who had used a topical ketoprofen-containing gel on the knees, but as the phlebography was negative, the patients were referred to our department. Many of these patients reported an increased light sensitivity in the ketoprofen-treated area after terminating the treatment, sometimes several months afterwards.

35 patients, 21 females (mean age 48.7 years, range 20–80 years) and 14 males (mean age 44.8 years, range 32–55 years) were referred to our clinic with suspected photoallergic or allergic reaction after having used a ketoprofen-containing gel. 3 of these patients have been reported earlier after the photoallergic contact dermatitis relapsed after the use of ketoprofen-contaminated objects as bandages and slippers (8).

### Test substances

The ketoprofen-containing gels Orudis<sup>®</sup> (Aventis Pharma, Stokholm, Sweden), Zon<sup>®</sup> (Antula, Stokholm, Sweden) and Siduro<sup>®</sup> (Iplex, Solna,

Sweden), all containing 2.5% ketoprofen, had been used by the patients. Ketoprofen was purchased from Sigma-Aldrich (Steinheim, Germany). Aventis Pharma kindly provided the constituents of Orudis<sup>®</sup> gel which besides ketoprofen are carboxypolymethylene, triethanolamine and lavender oil. The same ingredients except lavender oil is present in Siduro<sup>®</sup>. Fenofibrate was purchased from Sigma-Aldrich.

The Scandinavian photopatch test series (9) and petrolatum (pet.) preparations of benzophenone-3 (2-hydroxy-methylbenzophenone, Eusolex 4360), benzophenone-10 (hydroxy-methoxymethylbenzophenone, Mexenone) and benzophenone-4 (2-hydroxy-methoxybenzophenone-5-sulphonic acid, Sulisobenzon) were purchased from Chemotechnique Diagnostics, Sweden.

### Photopatch testing

All 35 patients were photopatch tested with the photopatch test series and at least 1 of the ketoprofen-containing gels and/or ketoprofen. 33 patients were photopatch tested with the ketoprofen-containing gel they had used. All but 1 patients were photopatch tested with a 10-fold serial dilution of ketoprofen (1.0%–0.0001% w/v) in ethanol while 1 patient was only tested with ketoprofen 1.0% w/v. All patients were photopatch tested with pet. preparations of carboxypolymethylene 2.0% w/w, lavender (*Lavandula angustifolia*) oil 1.0% w/w and triethanolamine 2.0% w/w. 26 patients were also photopatch tested with fenofibrate 10.0% w/w in pet. 30 patients were tested with benzophenone-3, 2.0% or 10.0% w/w in pet. 28 patients were tested with pet. preparations of benzophenone-4 and benzophenone-10 at 2.0% or 10.0% w/w and 5.0% or 10.0%, respectively. The photopatching was performed with small Finn Chambers<sup>®</sup> (Epitest Ltd Oy, Tuusula, Finland) which were applied to the skin on the back in duplicate as parallel columns. The patches were secured with Scanpor tape (Norgesplaster A/S, Vennesla, Norway) and remained for 24 hr on the back. They were then removed with a minimum of light exposure and with 1 side covered immediately with black cloth. The other side was irradiated with 5 J/cm<sup>2</sup> of broadband UVA (PUVA 4000, Photochemotherapy, Herbert Waldman, Werk für Lichttechnik, Germany). Reading was performed on day 3 according to ICDRG guidelines (11). A simultaneous contact allergy and photocontact allergy was present when there were positive reactions on both the non-irradiated and irradiated test sites and with a

substantially stronger reaction on the irradiated site (+++ versus +) (9).

Most of the patients were also patch tested with our standard test series. The results of this testing are reported elsewhere.

### Controls

167 patients who had been photopatch tested with the Scandinavian photopatch test series during a 20-year period served as controls.

### Statistical calculations

The rates of photocontact allergy to photosensitizers in the Scandinavian photopatch test series were compared between the ketoprofen patients and controls using 2-sided Fisher's exact test. The relationship between photocontact allergy to photosensitizers in the Scandinavian photopatch test series and various benzophenones on the 1 hand and degree of reactivity expressed as lowest concentration eliciting at least a + reaction in patients with photocontact allergy to ketoprofen when tested with serial dilutions of ketoprofen on the other was investigated with the Cochran-Armitage trend test.

### Results

In all 33 patients tested with their own ketoprofen-containing gel, photoallergic reactions to the gels were noted (Table 1). All 35 patients tested with the 4 ingredients of the gels tested positively to the irradiated ketoprofen. 2 patients had positive reactions to both ketoprofen and their own ketoprofen-containing gels on both the irradiated and the non-irradiated side. In these patients, the test reaction was significantly stronger on the irradiated side. 1 patient had positive patch test reaction to 1 more component, lavender oil, in the ketoprofen-containing gel used. No other positive photopatch test or patch test reactions were seen to the other components in the different ketoprofen-containing gels. The results of the photopatch testing with serial dilutions of ketoprofen are given in Table 1 and Fig. 1.

19 of 26 (73%) tested had positive photopatch test reactions to fenofibrate (Table 1). 6 of 30 (20%) tested had positive photopatch test reactions to benzophenone-3, 6 of 28 (21%) tested had positive photopatch test reactions to benzophenone-10 and none of 28 tested positively to benzophenone-4 (Table 1).

The results of the photopatch testing with the Scandinavian photopatch test series are given in Table 2. 26 (74%) had positive photopatch test reactions to fentichlor. In 3 of these patients,

Table 1. The results of photopatch testing with ketoprofen gel, ingredients of such gels, serial dilutions of ketoprofen and various benzophenones in 35 patients with photoallergic reactions from ketoprofen

| Patient number           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
|--------------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Test substance           | 1  | 2  | 3  | 4  | 5  | 6  | 7  | 8  | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 |    |    |
| Ketoprofen gel, as is    | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | pc | nt | p  | p  | p  | p  | p  | p  | p  | nt | p  | p  | p  | p  | p  | p  | pc |    |
| Carboxypolymethylene 2%* | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  |    |
| Triethanolamine 2%*      | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  |    |
| Lavender oil 1%*         | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | c  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  |    |
| Ketoprofen 1%#           | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | pc | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | pc |    |
| Ketoprofen 0.1%#         | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | nt | p  | –  | pc | p  | p  | p  | p  | p  | p  | p  | p  | p  | –  | p  | p  | p  | p  | p  | p  |    |
| Ketoprofen 0.01%#        | p  | p  | p  | p  | p  | p  | p  | p  | –  | –  | –  | p  | –  | p  | p  | p  | nt | p  | –  | p  | p  | p  | –  | p  | p  | p  | p  | p  | –  | –  | p  | p  | p  | p  | p  | p  | p  |
| Ketoprofen 0.001%#       | –  | p  | –  | –  | –  | –  | –  | –  | –  | –  | –  | p  | –  | p  | –  | –  | nt | –  | –  | p  | p  | –  | –  | p  | p  | p  | p  | –  | –  | –  | p  | p  | p  | p  | p  | p  | p  |
| Ketoprofen 0.0001%#      | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | nt | –  | –  | p  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  |
| Fenofibrate 10%*         | p  | nt | nt | nt | nt | nt | nt | p  | –  | –  | –  | p  | nt | p  | nt | p  | nt | p  | –  | p  | p  | p  | p  | p  | p  | p  | p  | p  | p  | –  | p  | p  | p  | p  | p  | p  | p  |
| Benzophenone-3 10%*      | p  | nt | –  | nt | nt | –  | –  | p  | –  | –  | –  | p  | nt | –  | –  | –  | nt | –  | –  | –  | –  | –  | –  | –  | p  | p  | –  | –  | –  | –  | p  | –  | –  | –  | –  | –  | –  |
| Benzophenone-10 2%*      | p  | nt | nt | nt | nt | nt | –  | nt | nt | nt | nt | nt | nt | nt | –  | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| Benzophenone-10 10%*     | nt | nt | nt | nt | nt | nt | –  | –  | –  | –  | –  | p  | nt | –  | nt | –  | nt | –  | –  | –  | p  | –  | –  | –  | –  | –  | p  | p  | nt | –  | –  | –  | –  | –  | –  | p  | nt |
| Benzophenone-4 5%*       | –  | nt | nt | nt | nt | nt | –  | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt | nt |
| Benzophenone-4 10%*      | nt | nt | nt | nt | nt | –  | nt | –  | –  | –  | –  | –  | nt | –  | nt | –  | nt | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | –  | nt | –  | –  | –  | –  | –  | –  | –  | –  |

c, contact allergic reaction; nt, not tested; p, photo allergic reaction and contact allergic reaction; pc, photo allergic reaction and contact allergic reaction; \*, in petrolatum; #, in ethanol.

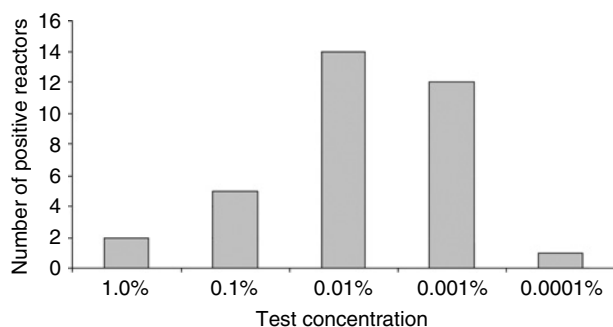


Fig. 1. The distribution of individual ketoprofen reactivity expressed as minimal eczematous dose (at least a + reaction) in 34 patients with photocontact allergy to ketoprofen photopatch tested with serial dilutions of ketoprofen.

there was simultaneous contact allergy to fentichlor. Positive photopatch test reactions to tetrachlorosalicylanilide and chlorpromazine hydrochloride were noted in 14 (40%) and 7 (20%) patients, respectively.

The simultaneous photocontact allergy to fentichlor, tetrachlorosalicylanilide and fenofibrate were statistically significantly overrepresented in the patients with the highest degree of reactivity to ketoprofen ( $P = 0.033$ ,  $0.035$ ,  $0.044$ , respectively) (Fig. 2, Tables 1 and 2). The higher degree of ketoprofen reactivity, the more likely a simultaneous photocontact allergy to fentichlor, tetrachlorosalicylanilide and fenofibrate. The chemical structures of the chemically defined photosensitizers being photopatch tested in the ketoprofen-photoallergic patients are given in Fig. 3.

Contact allergy to *Myroxylon pereirae* and fragrance mix was noted in 18 (51%) and 15 (43%) of the 35 patients, respectively (Table 2).

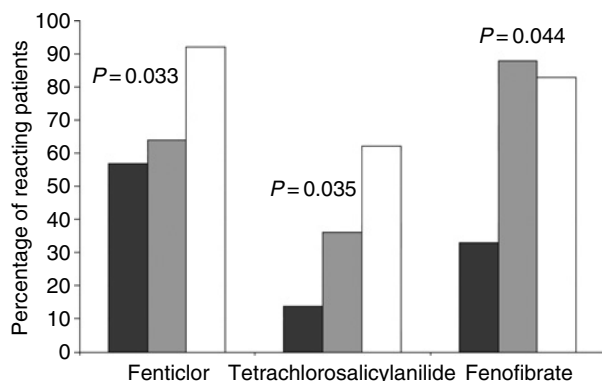


Fig. 2. The distribution of simultaneous photocontact allergy to fentichlor, tetrachlorosalicylanilide and fenofibrate with regard to degree of reactivity to ketoprofen in 34 patients photopatch tested with a serial dilution of ketoprofen (■, ketoprofen photoreactivity to 1% and/or 0.1%; ▒, ketoprofen photoreactivity to 0.01%; □, ketoprofen photoreactivity to 0.001% and/or 0.0001%).

The comparison of photocontact allergy rates between the ketoprofen patients and the controls is given in Table 3. There were statistically significantly more ketoprofen patients testing positively to promethazine hydrochloride, chlorpromazine hydrochloride, bithionol, fentichlor and tetrachlorosalicylanilide.

## Discussion

All 35 patients had positive photopatch test reactions to ketoprofen and the ketoprofen-containing gel when tested. 2 patients had reactions on both the irradiated and non-irradiated side of both ketoprofen and the ketoprofen-containing gel. The reaction on the irradiated side was significantly stronger than on the non-irradiated side (+++ reaction versus + reaction), indicating both a contact allergic and a photoallergic reaction to ketoprofen (9). Interestingly, with regard to the individual ketoprofen reactivity, these 2 patients had the highest degree of reactivity, i.e. 1 patient was the only 1 testing positively to ketoprofen at 0.0001% (1 ppm) and the other testing positively to 0.001% (Table 1). Even more interesting is the finding that the simultaneous contact allergy and photocontact allergy only could be demonstrated for the highest tested ketoprofen concentrations. Considering both these facts, 1 possible explanation for the demonstrated contact allergy to ketoprofen can be that it is false positive and instead a photoallergic reaction. The higher the degree of photoreactivity to ketoprofen the less unintentional UV irradiation is needed to result in a positive test. As other authors reporting contact allergy to ketoprofen (11, 12) either have not photopatch tested with ketoprofen or have not tested with ketoprofen dilutions, these reported contact allergies may also be false positive and represent photocontact allergy.

According to the other ingredients in the ketoprofen-containing gels, only 1 patient reacted with a contact allergic reaction to 1 more component in the gel, lavender oil which is a natural fragrance. Contact allergy to lavender oil has been reported in 3 Belgian patients photoallergic to ketoprofen (7). Our patient with lavender oil allergy was also contact allergic to *Myroxylon pereirae* and fragrance mix, like many of the other ketoprofen patients. Linalool, which is a major ingredient in lavender oil, is a sensitizer when oxidized (13). It is not present in fragrance mix neither described as an ingredient in *Myroxylon pereirae* (14). On the other hand, simultaneous contact allergy to fragrance mix and *Myroxylon pereirae* has been reported in

Table 2. The results of photopatch testing with Scandinavian photopatch test series with 35 patients with photoallergic reactions from ketoprofen

| Test substance*                   | Patient number |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
|-----------------------------------|----------------|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|
|                                   | 1              | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 |   |
| Trichlorocarbanilide 1%           | -              | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | - |
| Promethazine hydrochloride 1%     | p              | p | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | p  | -  | -  | -  |   |
| 4-Aminobenzoic acid (PABA) 10%    | -              | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |   |
| Tribromsalicylanilide 1%          | -              | - | - | p | p | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |   |
| Chlorpromazine hydrochloride 0.1% | p              | p | - | p | - | - | p | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | p  | -  | -  | -  | p  | -  | -  | -  | -  |   |
| 6-Methylcoumarin 1%               | -              | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |   |
| Bithionol 1%                      | p              | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | p  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |   |
| Fentichlor 1%                     | p              | p | p | p | p | - | p | - | - | p  | p  | p  | p  | p  | p  | -  | p  | pc | -  | p  | pc | -  | pc | p  | p  | p  | p  | p  | p  | -  | -  | p  | p  | p  | -  | p |
| (+)-Usnic acid 0.1%               | -              | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |   |
| Atranorin 0.1%                    | -              | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |   |
| Wood mix 20%                      | -              | - | - | - | - | - | - | - | - | -  | -  | p  | -  | -  | -  | -  | -  | -  | -  | -  | c  | -  | c  | -  | -  | p  | -  | -  | -  | -  | -  | c  | -  | -  | -  |   |
| Evermic acid 0.1%                 | -              | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |   |
| Myroxylon pereirae 25%            | c              | c | - | c | - | - | c | - | - | -  | -  | c  | -  | -  | -  | c  | -  | -  | -  | c  | c  | c  | c  | c  | c  | -  | c  | -  | -  | -  | -  | c  | c  | -  | c  |   |
| Tetrachlorosalicylanilide 0.1%    | p              | - | p | p | - | p | - | p | - | -  | -  | p  | p  | p  | -  | -  | -  | -  | p  | p  | p  | -  | -  | -  | p  | p  | p  | -  | -  | -  | p  | c  | p  | -  | p  |   |
| Hexachlorophene 1%                | -              | - | - | - | - | - | - | - | - | -  | -  | p  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |   |
| Chlorhexidine digluconate 0.5% aq | -              | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |   |
| Triclosan 2%                      | p              | - | - | - | - | - | - | - | - | -  | -  | p  | -  | -  | -  | -  | -  | -  | -  | p  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | c  | -  | -  | -  |   |
| Diphenhydramine hydrochloride 1%  | -              | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |   |
| Fragrance mix 6%                  | c              | c | - | c | c | - | - | p | - | c  | -  | c  | -  | c  | -  | -  | -  | -  | -  | c  | c  | c  | -  | c  | -  | -  | -  | -  | c  | -  | -  | c  | -  | -  | c  |   |

c = contact allergic reaction; nt = not tested; p = photo allergic reaction; pc = photo allergic reaction and contact allergic reaction; \* = vehicle is petrolatum unless otherwise indicated.

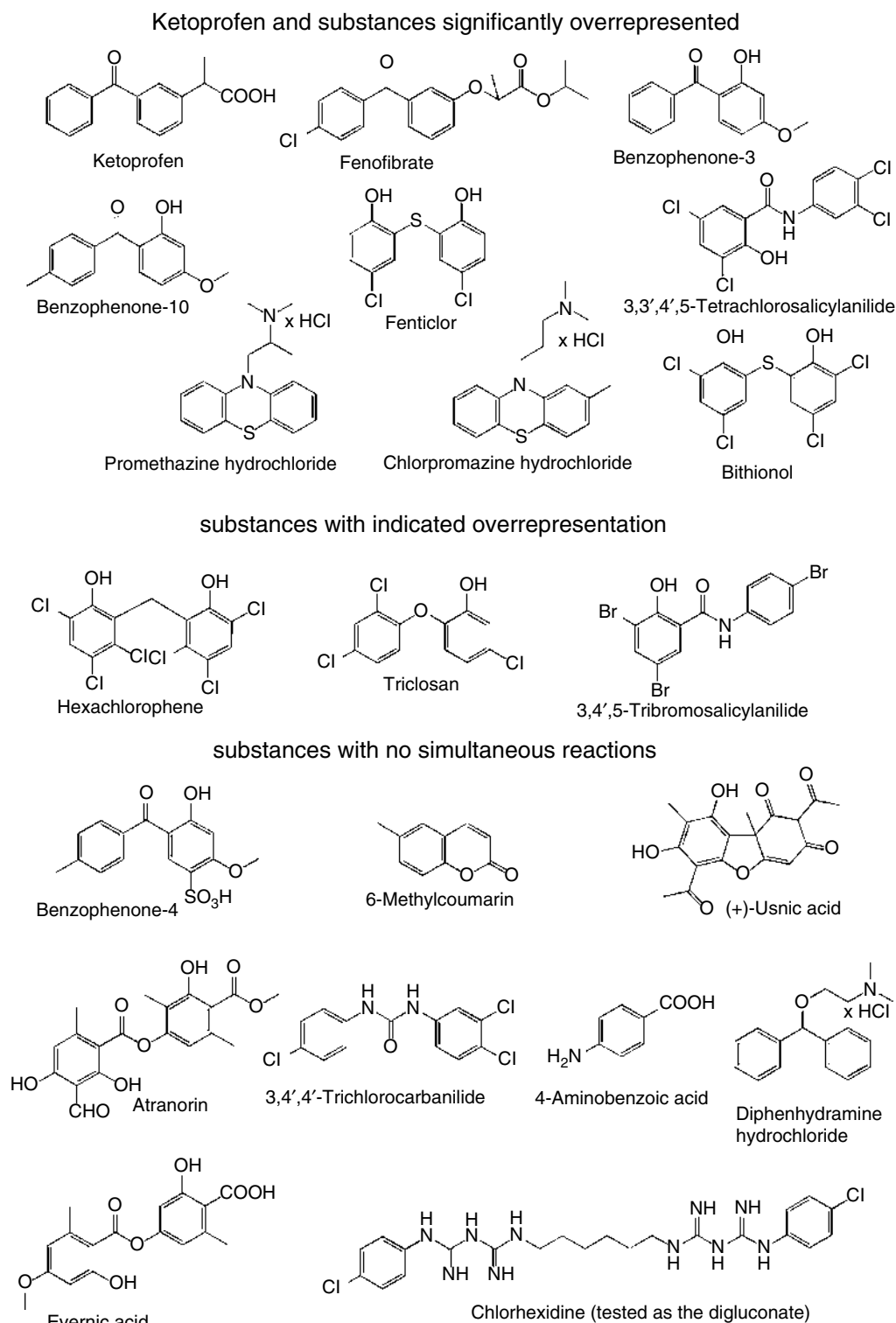


Fig. 3. Structures of chemically defined substances photopatch tested in 35 patients with photocontact allergy to ketoprofen.

patients photoallergic to ketoprofen (7, 15–18). Cinnamic aldehyde that is a component of both fragrance mix and *Myroxylon pereirae* has been suggested to explain this phenomenon (18). However, when 8 of our patients were patch tested with the separate fragrance mix

ingredients, an overrepresentation was noted to cinnamic alcohol (19) and not to cinnamic aldehyde (18).

The demonstrated simultaneous photocontact allergies to various benzophenones including fenofibrate may represent cross-reactions as the

Table 3. The number of positive reactions in 35 ketoprofen patients and 167 controls photopatch tested with the Scandinavian photopatch tests series as well as the comparison of photocontact allergy rates using 2-sided Fisher's exact test

| Photo-patch test substances   | Ketoprofen patients ( <i>n</i> = 35) |    | Standard photo-patch-tested patients ( <i>N</i> = 167) |     | Difference<br>p-value |
|-------------------------------|--------------------------------------|----|--------------------------------------------------------|-----|-----------------------|
|                               | <i>n</i>                             | %  | <i>n</i>                                               | %   |                       |
| Trichlorocarbanilide          | 0                                    | 0  | 0                                                      | 0   |                       |
| Prometazine hydrochloride     | 4                                    | 11 | 4                                                      | 2.4 | 0.032                 |
| 4-Aminobenzoic acid           | 0                                    | 0  | 0                                                      | 0   |                       |
| Tribromsalicylanilide         | 2                                    | 6  | 1                                                      | 0.6 | 0.078                 |
| Chlorpromazine hydrochloride  | 7                                    | 20 | 0                                                      | 0   | 0.001                 |
| 6-Methylcoumarine             | 0                                    | 0  | 1                                                      | 0.6 | 1.0                   |
| Bithionol                     | 2                                    | 6  | 0                                                      | 0   | 0.029                 |
| Fenticlor                     | 26                                   | 74 | 3                                                      | 1.8 | 0.0000                |
| (+)-Usnic acid                | 0                                    | 0  | 1                                                      | 0.6 | 1.0                   |
| Atranorin                     | 0                                    | 0  | 1                                                      | 0.6 | 1.0                   |
| Wood mix                      | 2                                    | 6  | 2                                                      | 1.2 | 0.1                   |
| Evernic acid                  | 0                                    | 0  | 0                                                      | 0   |                       |
| Myoxylon pereirae             | 1                                    | 3  | 4                                                      | 2.4 | 1.0                   |
| Tetrachlorosalicylanilide     | 14                                   | 40 | 0                                                      | 0   | 0.0000                |
| Hexachlorophene               | 2                                    | 6  | 1                                                      | 0.6 | 0.07                  |
| Chlorhexidine digluconate     | 0                                    | 0  | 0                                                      | 0   |                       |
| Triclosan                     | 3                                    | 9  | 3                                                      | 1.8 | 0.06                  |
| Diphenhydramine hydrochloride | 0                                    | 0  | 0                                                      | 0   |                       |
| Fragrance mix                 | 1                                    | 3  | 1                                                      | 0.6 | 0.3                   |

structures are similar (Fig. 3). Fenofibrate is an antilipemic agent and has been reported to induce photosensitization (20). Cross-reactivity between ketoprofen and fenofibrate has been reported earlier (20) as well as between ketoprofen on the 1 hand and benzophenone-3 and benzophenone-10 on the other (8, 20). However, no positive reactions were noted to benzophenone-4, which is in agreement with a recently published observation (7). On the other hand, from a structural point of view, it is very hard to understand and explain the simultaneous photocontact allergies to fenticlor, chlorpromazine, bithionol, tetrachlorosalicylanilide and promethazine (Table 2). Such simultaneous photocontact allergies to ketoprofen, fenticlor and tetrachlorosalicylanilide, respectively, have been reported (15, 17). In this study, we found even higher frequencies of positive photopatch test reactions to fenticlor and tetrachlorosalicylanilide than previously reported (15, 17). Interestingly, these simultaneous photocontact allergies to fenticlor, tetrachlorosalicylanilide and fenofibrate appear mainly in those with a higher reactivity to ketoprofen, the higher reactivity the more likely a simultaneous photoallergy (Fig. 2).

On the whole, multiple photocontact allergies are common when photopatch testing (21). We wanted therefore to compare the pattern of simultaneous photocontact allergies in our ketoprofen population with those having been photopatch tested with the Scandinavian photopatch test series the last 20 years before the

introduction of topical treatment with ketoprofen in Sweden. Surprisingly, there are highly statistically significant differences in the photocontact allergy rates for fenticlor, tetrachlorosalicylanilide and chlorpromazine but also statistically significant differences for bithionol and promethazine (Table 3).

26 (74%) of the ketoprofen patients had a positive photopatch test reaction to fenticlor. Since 1982, 167 patients have been photopatch tested in Malmö, besides these 35 ketoprofen patients. Of these, compared to 167 patients, only 3 (1.8%) patients had positive photopatch test reactions to fenticlor (Table 3). Thus, a simultaneous photocontact allergy to fenticlor is significantly overrepresented in those with a photocontact allergy to ketoprofen.

14 (40%) of the ketoprofen patients were also positive to tetrachlorosalicylanilide. 1 patient had positive reactions on both irradiated and non-irradiated side, indicating a contact allergic reaction (Table 2). Of the 167 previously photopatch tested patients, mentioned above, none were found to have a contact allergy or a photocontact allergy to tetrachlorosalicylanilide (Table 3). Tetrachlorosalicylanilide belongs to the family halogenated salicylanilides and is used as an antimicrobial agent. It has been prohibited in Europe since the 1970s (15) but is still available in US (22).

In summary, ketoprofen is a potent photosensitizer with many simultaneous photocontact allergies to various photosensitizers, some of which have structural similarities.

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