Review paper

Photosensitivity to selected topical nonsteroidal anti-inflammatory drugs preparations – a review of literature data and author's own experience

DOROTA JENEROWICZ, OLIWIA JAKUBOWICZ, ADRIANA POLAŃSKA, ANNA SADOWSKA-PRZYTOCKA, ALEKSANDRA DAŃCZAK-PAZDROWSKA, RYSZARD ŻABA

Department of Dermatology, Poznan University of Medical Sciences, Poznan, Poland

Abstract

Ketoprofen and diclofenac, which belong to the group of nonsteroidal anti-inflammatory drugs (NSAIDs), are widely used mediactions due to their well known anti-inflammatory effect. Most adverse reactions to these drugs are associated with gastroinstestinal track and kidney, moreover, numerous date indicate that also topical use of ketoprofen and diclofenac may lead to side effects, especially to photosensitivity reactions. Photosensitivity includes common phototoxic reaction as well as much more rare photoallergic reaction, which is an example of delayed T cell mediated hypersensitivity. Useful methods to diagnose photosensitivity reaction include patch testing and photopatch testing. The aim of this study was to present up-to-date knowledge on patomechanism of NSAID-induced photosensitivity, their clinical manifestations and management including recommendations of European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP). The authors also report 4 cases of suggestive photoallergic contact dermatitis after topical use of NSAID in patients diagnosed and treated in the Department of Dermatology, Poznan University of Medical Sciences, together with photographic documentation.

Key words: *ketoprofen, diclofenac, photosensitivity, photoallergic contact dermatitis.*

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the treatment of pain and various inflammatory disorders, and account for around 5% of all National Health Service prescriptions in Great Britain [1]. According to data from the United States, NSAIDs are regularly used by 10-20% of population above 65 years of age. In our country currently around 4 million patients are treated with NSAIDs [2].

Safe use of NSAIDs is markedly restricted by the high incidence of adverse events, particularly concerning gastrointestinal tract and kidneys. Moreover, paradoxically for NSAIDs is that they are designed to alleviate inflammatory responses, but may cause severe inflammation when combined with sunlight exposure [3, 4]. Nonsteroidal anti-inflammatory drugs as a group differ in chemical structure but are consistent in their ability to inhibit cyclooxygenase enzymes, regarded as markers of inflammatory state [4, 5].

Among various NSAIDs, particularly ketoprofen and diclofenac have been associated with photosensitivity reactions. The drugs are currently used orally, intramuscularly, intravenously and rectally. Ketoprofen was introduced as an oral drug in the 1970s, and subsequently, in the 1980s, topical patch and gel delivery systems were developed. Topical medication is nowadays used in more than 70 countries [6]. Currently, in Poland ketoprofen is applied topically as a 2.5% gel and diclofenac may be applied as a 1% gel. Topical formulations of ketoprofen and diclofenac are used to

Correspondence: Dorota Jenerowicz, Department of Dermatology, Poznan University of Medical Sciences, Przybyszewskiego 49, 60-355 Poznan, Poland, e-mail: djenerowicz@yahoo.com

treat symptoms of pain and inflammation in conditions such as minor trauma (sprains, bruising), tendonitis, small-joint osteoarthritis, ankylosing spondylitis, rheumatoid arthritis or phlebitis. Furthermore in 2001, a novel formulation containing 3% diclofenac dissolved in a gel containing 2.5% hyaluronate has been licensed as a topical treatment for actinic keratoses with the best clinical cure rates (58–85%) observed when the product is administered at least for 90 consecutive days [7].

Patomechanisms of nonsteroidal anti-inflammatory drugs – induced photosensitivity

Drug-induced photosensitivity is associated with the combination of the administration of certain drugs and subsequent sunlight exposure. Patient's response is manifested through complex biochemical changes occurring in the tissue after the sunlight absorbance by exogenous substance as the first step. Photosensitivity is a general term describing either the common phototoxic response or the much more rare photoallergic reaction. While a differentiation between these two types of photosensitivity reactions may be difficult, some principles may be established, based on clinical presentation and anamnesis [3, 8].

Phototoxicity is associated with the absorption of light energy. It can occur in anybody exposed to enough light energy in the presence of photosensitisers within the skin. Drugs, either absorbed locally into the skin or via the systemic circulation, may serve as an object of a photochemical reaction, which may lead directly to chemically induced photosensitivity reactions or to an enhancement of the usual effects of sunlight [8, 9].

Patomechanism of phototoxic reactions induced by NSAIDs – particularly to ketoprofen has been studied by various researchers. According to Bosca *et al.* [10], ketoprofen phototoxicity probably results from the production of short-lived intermediate products such as free radicals rather than from toxic photoproducts. Moreover, according to Constanzo *et al.* [11], ketoprofen irradiation promotes the photolysis of erythrocyte suspensions. Marked cell-membrane damage induced by this photohaemolysis was found to take place by both oxygen-dependent and oxygen independent mechanisms. Addition of radical scavengers (reduced glutathione, superoxide dismutase, mannitol) was found to significantly decrease photohaemolytic reactions, suggesting the involvement of free radicals in this process. To summarize, mentioned data indicate that significant part of phototoxicity induced by ketoprofen arises from photosensitized damage of cell membranes via radical intermediates [3]. Bosca *et al.* [12] suggest, that ketoprofen is able to induce photoperoxidation of linoleic acid. Lipid peroxidation is one of the most important examples of damage induced in aerobic cells by oxidants – it is harmful to cell membrane structure and function and has been linked to an increase in ion permeability, loss of fluidity, cross-linking of aminolipids and polypeptides, and inactivation of membrane enzymes and receptors.

Another possible patomechanism of ketoprofen phototoxicity is DNA damage. According to Chouini-Lalanne *et al.* [13], ketoprofen may induce DNA damage *in vitro* upon irradiation and photosensitise the formation of pyrimidine dimmers and single strand breaks. Authors suggest, that the extent of DNA damage due to NSAID photosensitization depends on the structure of the drug and the kind of damage involved. Among various NSAIDs, particularly arylpropionic acid derivatives (ketoprofen and tiaprofenic acid) promote formation of more dimers than those observed by irradiation of DNA alone. Their ability to form thymine dimers, which are one of the major lesions of DNA following UV irradiation, make such photosensitisers particularly harmful.

Photoallergy is an example of delayed T cell mediated hypersensitivity response involving immunological reaction. It may occur after topical exposure to drugs and is also characterised by possible ectopic cutaneous responses and generalised reactions following systemic administration of suspicious medication. The reaction requires previous sensitisation and is characterized by a latency period. Lesions may be polymorphic, but usually they have an eczematous appearance. Unlike in phototoxic reactions, here skin lesions may extend to nonirradiated areas, and the reaction is dose-independent [8, 14].

It is suggested, that an initial step in the induction of delayed type hypersensitivity is the uptake of a hapten applied to the skin by antigen-presenting cells within the epidermis. Animal studies with the use of photohaptens (ketoprofen) supported the above mechanism [14, 15]. Subsequently a migration of antigen-presenting cells takes place via lymphatics to the local draining lymph nodes, where they stimulate the proliferation of antigen specific T lymphocytes – this mechanism has also been confirmed by Gerberick *et al.* [16, 17] based on murine studies after exposure to tetrachlorosalicylanilide (TCSA) in combination with UVA radiation.

Clinical manifestation of drug-induced photosensitivity reactions

A phototoxic reaction typically starts immediately and resembles an exaggerated sunburn. Skin lesions appear on exposed areas, giving a clear delineation of shading caused by clothing. Patients may complain on burning sensation and pain, rather than itching. All phototoxic responses are dependent on the dose of photosensitiser and the intensity of sunlight experienced [3, 8].

As it was mentioned earlier, a photoallergic reaction has an immunological basis and requires previous exposure to the photosensitising agent. Patients who experience photoallergic responses may present 1 to 14 days after expo-

sure to sunlight with papulovesicular eruption, marked pruritus, and eczematous skin lesions [8, 14].

Management of photosensitivity reactions

Intensive treatment and proper skin care are especially needed during an acute phase of the reaction. In case of a suspected phototoxic reaction, the treatment is usually the same as would be applied to acute sunburn. Usually within 24 to 48 hours stinging and burning sensation decreases and some relief may be achieved with topical glucocorticosteroids and soothing creams, gels and emollient preparations. Antibacterial creams should be applied to prevent infection, particularly in case of bullae formation with subsequent rupture and erosions. Avoidance of the offending photosensitising agent and/or sunlight exposure is clearly required. Antihistamines and glucocorticosteroids may be required to treat inflammation arising from photoallergic reactions [2, 3]. Antioxidant therapy is suggested as a valuable approach in shock, inflammation and ischaemia/reperfusion injury [18, 19]. Antioxidants may be administered in many ways – as a diet bioflavonoid components with high vegetable and fruit content, or as supplements of vitamins A, C and E, and specific plant extracts (for example grape seed).

In many cases, drug-induced photosensitivity may be diagnosed without specific investigations, particularly if the onset can be associated with the start of a course of therapy with a drug of known photoactivity. To confirm relevance of suspected drug in photosensitivity reaction patch testing and photopatch testing is used. Patch testing has been used extensively for the diagnosis of contact allergy and to confirm sensitivity in patients with delayed-type reactions [14, 20, 21]. It consists of application of the suspected agent (hapten) on the skin with occlusive dressing and the subsequent reading of dermatological reactions (after 48 h and 96 h or even longer). Currently, the most effective and widely used method for investigating photoallergic contact dermatitis in a patient is to perform photopatch testing. The test is expected to reproduce a photosensitization reaction after application of the suspect agent on the skin under a defined spectrum of irradiation [22].

During photopatch testing, agents under investigation are prepared in a vehicle (most often white petrolatum) and a small volume is placed within plastic or metal chambers, which have low chemical reactivity and are mounted on hypoallergenic adhesive tape on the skin of the back. Tape and chambers should not be placed on the paravertebral area 5 cm on either side of the midline, but should be placed lateral to this area on the left and/or right sides. After a variable period of time, the tape and chambers are removed and the skin at the site of one set is irradiated with a UV source. At variable times after irradiation (usually multiples of 24 h), both test sites are then evaluated and the strength and characteristics of any reaction is recorded using a grading scale. The process of photopatch testing involves several variable steps and that is why it lacks unified characteristics and methodologies differ between specialists and centers [14]. Quite recently, Marmgren *et al.* [23] published a study determining whether a reduction in occlusion time from 24 h to 1 h (in order to simplify the testing procedure) influences test results when photopatch testing with ketoprofen. A total of 22 patients with a known or suspected photoallergy to ketoprofen were simultaneously photopatch tested with ketoprofen using both 1 h and 24 h occlusion. One side of the patient's back was irradiated with 5 J/cm^2 UVA, and the other side was covered. Measurements were made after 3 days on both irradiated and non-irradiated sides. A total of 20 controls were photopatch tested with ketoprofen using 1 h occlusion. All of the patients showed positive reactions on the irradiated side. No positive reactions were observed on the non-irradiated side. All controls were negative. Authors conclude, that 1 h occlusion time may be sufficient to establish photo-contact allergy to ketoprofen. The results however apply only to ketoprofen and further studies are needed to determine whether a similar approach can be used with other components of photopatch test series.

When photopatch testing NSAIDs, possible cross-reactivity has to be taken into consideration. Cross-reactions have been reported between ketoprofen and chemically related benzophenone moiety-containing molecules, including the sunscreen benzophenone-3 and fenofibrate [24, 25]. The thiophene-phenylketone part of another arylpropionic derivative, tiaprofenic acid is similar to the benzophenone moiety and may explain why cross reactions are more common between tiaprofenic acid and ketoprofen, than the other arylpropionic acid derivatives such as ibuprofen or naproxen [26]. Foti *et al.* [27] investigated 15 subjects with allergic contact dermatitis and photoallergic contact dermatitis to ketoprofen and tested them with the use of SIDAPA (Società Italiana di Dermatologia Allergologica Professionale e Ambientale) patch test standard series, including fragrance mix and its components (eugenol, isoeugenol, oak moss, geraniol, hydroxycitronellal, amylcinnamaldehyde, cinnamyl alcohol and cinnamaldehyde) and with the SIDAPA photopatch test series. Allergic reactions to cinnamyl alcohol were noted in all patients, whereas some patients also showed positive reactions to fenticlor, octocrylene and benzophenone-10. Computerized conformational analysis demonstrated that the structure of cinnamyl alcohol is similar to that of ketoprofen, whereas the structures of benzophenone-10, octocrylene and fenticlor are completely different. Authors suggest, that in patients with contact allergy to ketoprofen, concomitant positive reactions to cinnamyl alcohol are due to cross-sensitization, whereas simultaneous allergic reactions to fenticlor, octocrylene and benzophenone-10 should be regarded as co-sensitizations.

It has to be emphasized, that photosensitivity reactions can be minimised by avoidance of the combination of sun-

light and a photosensitising drug. Proper protective clothing, eyewear and systematic application of a sunscreen characterized by high protection rating are the most important measures that can be introduced, particularly if some exposure to UV radiation, due to patients daily routine is hard to avoid [3].

Photosensitivity reactions to selected nonsteroidal anti-inflammatory drugs – review of authors' own experience and published literature data

The authors would like to present 4 cases of suggestive photoallergic contact dermatitis after topical use of NSAID (3 from ketoprofen, 1 from diclofenac) in patients diagnosed and treated in the Department of Dermatology, Poznan University of Medical Sciences. The clinical date of patients are summarized in Table 1. All patients were nonatopic and denied any adverse reaction to systemic topical anti-inflammatory drugs, including ketoprofen, in the past. Also there was no history of polymorphic drug eruption. In all cases skin lesions were restricted to the site of application of drug and had an eczematous picture with formation of bullous lesions in 2 patients (patient number 1 and 2). All patients complained of intense itch within the area of skin lesions. The delay between the application of NSAID and the reaction was between 2 and 60 days. One patient (patient number 3) experienced the recurrence of skin lesions in relation to sun exposure after 1 year of previous episode. The skin lesions were located at the site of initial area of application and appeared despite the use of sunblockers. Ketoprofen-induced skin lesions are presented in Figures 1-3, Figure 4 presents skin lesions provoked by diclofenac.

In the literature there is data concerning photosensitivity reactions mainly to ketoprofen and diclofenac. In 1983 Valsecchi *et al.* reported the first case of allergic dermatitis from the topical use of ketoprofen, while two years later Spanish researcher published the first description of photoallergic contact dermatitis [28, 29]. Since then, increasing numbers of similar cases were presented in literature [6, 30, 31]. In the report of 4 cases of photocontact dermatitis from Japan, photopatch testing with ketoprofen and other cross-reactive NSAID were performed (tiaprofenic acid and suprofen). All cases had positive results with ketoprofen, while 3 of 4 also reacted to tiaprofenic acid. In all patients skin biopsy was also taken and only in one patient, 17 days after the discontinuation of the use of poultice with ketoprofen, the accumulation of drug was found in the area of previously affected skin [30].

Researchers from Spain presented an interesting case of a 30-year-old man with intensely itchy lesions within palmar area of hands and fingers after 3 days after applying a gel containing piketoprofen to his spouse's neck and following sun exposition. According to the authors, this was an example of so called 'consort contact dermatitis', defined as allergic dermatitis caused by contact with environmental sensitizers borne by a partner. Diagnostic procedures were perfomed and photopatch tests revealed positive reaction to piketoprofen, ketoprofen as well as dexketoprofen [32].

Devleeschouwer *et al.* [33] investigated photocontact allergic reaction to ketoprofen in the group of 42 patients. They performed patch tests and photopatch tests and confirmed photoallergic contact dermatitis in 38 patients. The first skin eruption in the analyzed group was observed after the average of about 15 days (varied between 1 and even 63 days) and in 67% cases skin lesions were detected also outside the region of application. In the same time, authors investigated the presence of prolonged photosensitivity and found that 30% of cases had a history of the recurrence of skin lesions. After having stopped the application of ketoprofen, skin reactions in relation to sun exposure were mostly observed between 1 and 8 weeks, but in one case even up to 14 years. Another description of prolonged photosensitivity secondary to contact photoallergy to topical ketoprofen was published by Albes *et al.* [34]. A 46-year-old female had an episode of papulovesicular eruption on her right ankle 8 days after topical us of ketoprofen and she also suffered from regular erythematous eruptions after short UV exposure (even in winter) without concomitant application of drug during the next year. We have also detected prolonged

Table 1. Summary of clinical cases presented by the authors

Case number	Gender	Age (years)	Reaction onset time (days)	Location of skin lesions	Suspected drug	Reason for using drug
1	male	38	2	upper extremities	ketoprofen gel	joint pain
2	male	57	60	left lower leg	ketoprofen gel	adjuvant therapy after fracture of the metatarsal bones of the left hand
3	male	21	14	left foot	ketoprofen gel	joint pain
4	male	29	7	right foot	diclofenac gel	joint pain

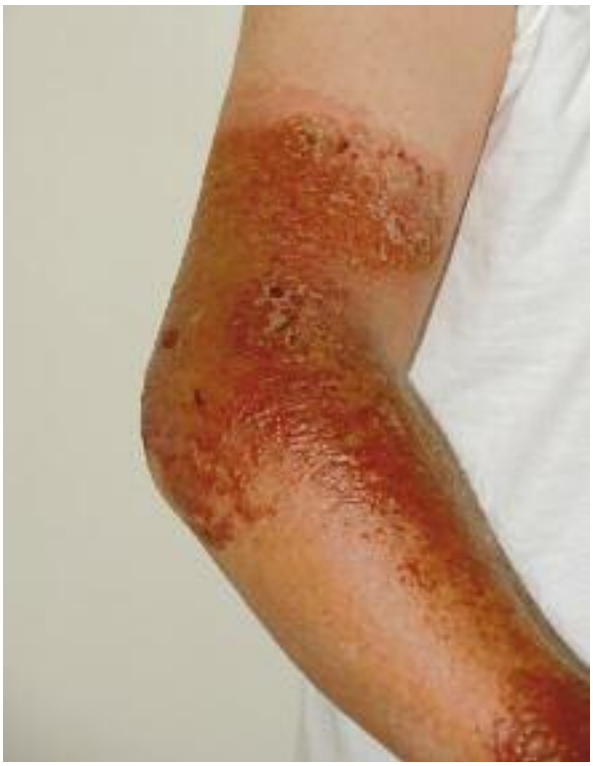

Fig. 1. Disseminated skin lesions in 38-year-old patient after application of ketoprofen gel

photosensitivity in one of 4 our patients. Patient number 4 experienced the recurrence of eczematous eruption at the site of previous reaction after 1 year. The second episode was observed after sun exposure, but without taking any topical or systemic NSAID during the last year.

Recent data provides the description of two cases of photodermatitis caused by oral ketoprofen in patients with

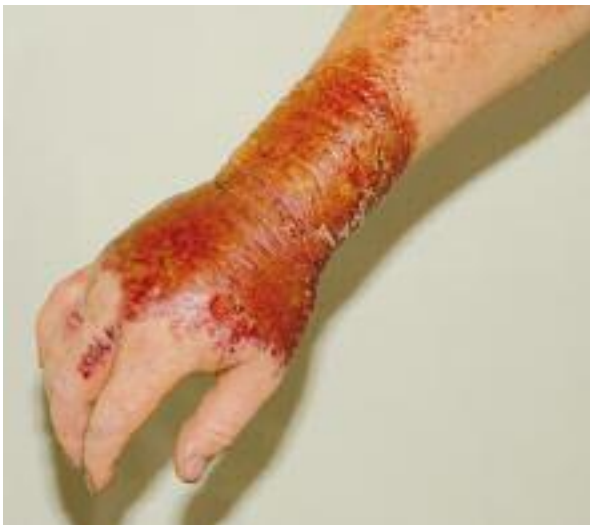

Fig. 2. Disseminated skin lesions in 38-year-old patient after application of ketoprofen gel

previous skin reactions to ketoprofen gel. Both patients experienced eczematous reactions (one localized and one disseminated) due to the oral intake of ketoprofen and both in the past had episodes sugestive of photoallergic contact dermatitis after the application of this drug in the form of gel and subsequent UV irradiation. The authors highlight the possibility of a photoinduced reaction after systemic administration of ketoprofen in patients with a history of contact allergy to this drug [35].

In the literature there are numerous described cases of allergic contact dermatitis to diclofenac, whereas photosensitivity reactions were reported only few times [7, 36-41]. To our knowledge, the first case report of photoallergic contact dermatitis due to diclofenac was published in 2003 [40]. Spanish researchers observed acute vesicular

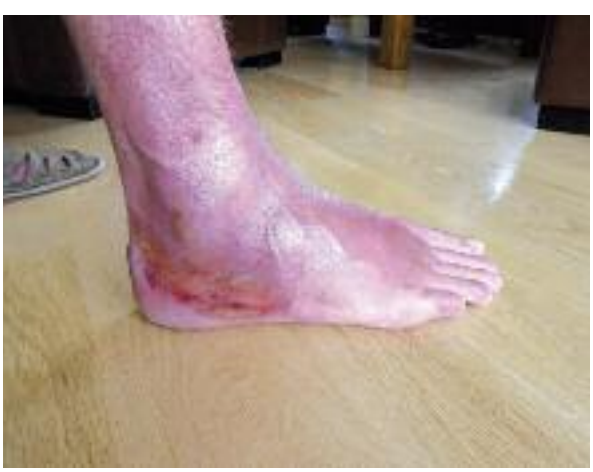

Fig. 3. Skin lesions after application of preparation containing ketoprofen in 21-year-old patient

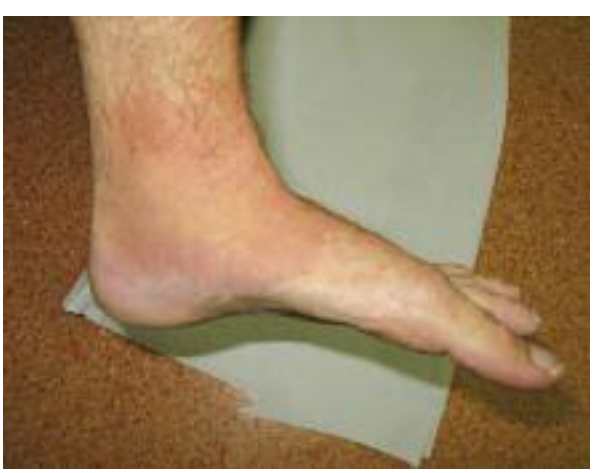

Fig. 4. Skin lesions after application of preparation containing diclofenac in 29-year-old patient

eczema within the elbow of a 40-year-old man after application of diclofenac. This adverse reaction occurred in summer and was probably the second episode of photoallergic contact dermatitis in patient's life. Patch tests were made and revealed positive reaction to diclofenac, while to other NSAID, like ketofrofen, where negative [40].

Fernández-Jorge *et al.* [32] published two case reports of photoallergic contact dermatitis triggered by diclofenac which presented as a cross-reaction to aceclofenac. Patients presented positive patch tests results both to diclofenac and aceclofenac. What is interesting, one of the described patients experienced eczematous eruption even several hours after sun exposure.

In 2006 German authors presented a case demonstrating a photoallergic contact dermatitis to diclofenac as the active ingredient in a gel formulation accepted for treatment of actinic keratoses [7]. A 77-year-old woman was treated with 3% topical diclofenac due to the superficial actinic keratosis on the right cheek and after 7 weeks of therapy she experienced stinging erythema at the area of application. Patch tests and photopatch tests revealed positive results to diclofenac and commercial gel preparation [7]. Taking into account long treatment with this preparation (even during vacation) and the occurrence of actinic keratoses on sun exposed areas, the possibility of photoallergic reactions should be always monitored.

Topical ketoprofen preparations and European Medicines Agency statement

Topical NSAIDs preparations (ketoprofen in particular), have been under thorough review of the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) due to concerns over the risk of skin photosensitivity reactions, including photoallergy, and a new risk of co-sensitisation with octocrylene (a chemical sun filter included in several cosmetic and care products) [42]. Analysis of all the available safety data, including data from EU member states' databases and data provided by involved manufacturers, allowed to conclude, that the risk of serious photoallergic reactions was very low (1 case per 1 million patients treated) and that this risk may be minimised by harmonised risk-minimisation measures, including the following:

- the drugs should no longer be available over the counter but should only be obtained with a prescription from a physician,
- strengthened warnings on sun exposure should be included in the product information, as well as information on adverse skin reactions when topical ketoprofen is used together with octocrylene,
- the risks of photoallergy with topical ketoprofen and the way to prevent it should be clearly communicated to healthcare professionals and to patients,
- doctors, pharmacists and patients should be aware of the risk of photoallergy with topical ketoprofen,
- doctors should tell their patients how to use topical ketoprofen-containing medicines appropriately,
- patients should make sure that the treated areas are protected from sunlight during the whole period of ketoprofen treatment and the two weeks after stopping the treatment; they should also wash their hands carefully after each application of ketoprofen,
- patients should discontinue treatment immediately if they develop any skin reaction after application of these medicines, and seek their doctor's advice,
- patients who have any questions should speak to their doctor or pharmacist.

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