

## Review Article

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# Ketoprofen-induced photoallergic dermatitis

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**Drug-induced photosensitivity reactions are significant adverse effects. Ketoprofen is one of the most common drugs that can cause skin rash in sun-exposed areas. Non-steroidal anti-inflammatory drugs (NSAIDs), such as ketoprofen, are often used for a variety of symptoms, including pain and fever. An understanding of the presentation and clinical course of ketoprofen-induced photosensitivity is necessary to correctly diagnose and manage this condition. Ketoprofen-induced photosensitivity reactions usually present as photoallergic dermatitis, which is a cell-mediated immune process. The benzophenone moiety in ketoprofen plays a major role in ketoprofen's ability to act as a photosensitizer. Several agents, such as fenofibrate and octocrylene have been found to be associated with aggravation of ketoprofen-induced photoallergic dermatitis or cross-photosensitization, and these reactions result from structural similarities with ketoprofen. Treatment of ketoprofen-induced photoallergic dermatitis includes discontinuation of ketoprofen, topical or systemic corticosteroids and avoidance of sun exposure and agents known to exacerbate dermatitis. In conclusion, photoallergic dermatitis is a significant adverse effect of ketoprofen. Some agents known to worsen dermatitis may be found in sun protection products (notably, octocrylene in sunscreen). Educating the patient to avoid these products is critical to treatment. Since NSAIDs, such as ketoprofen, are used commonly for a variety of illnesses, drug-induced photoallergic dermatitis should be high on the differential in individuals using these medications who present with acute onset of a rash in sun-exposed areas.**

**Key words** Anti-inflammatory - dermatitis - gel - ketoprofen - non-steroidal - photoallergic - photosensitize - radiation - topical - ultraviolet

## Introduction

Photodermatoses can be acquired or congenital. Examples of associated conditions include systemic lupus erythematosus, dermatomyositis, xeroderma pigmentosum and cutaneous porphyria<sup>1,2</sup>. In addition to these diseases, photodermatoses may also occur as a reaction to medications<sup>3</sup>.

Drug-induced photosensitivity is a common problem that may be encountered with a variety of medications. The list of agents known to cause

photosensitivity is extensive. Antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, retinoids, hypoglycaemics and anticonvulsants are notable examples of drugs that can cause dermatoses in sun-exposed areas<sup>4-8</sup>.

## Photodermatoses - medication associated

Photodermatoses due to medication usage may be classified into two categories: phototoxic and photoallergic reactions<sup>9-11</sup>. Both require a topical or systemic sensitizer and exposure to ultraviolet

radiation (UVR), but the mechanisms through which these processes induce dermatitis differ<sup>12-14</sup>.

**Phototoxic reactions:** Phototoxic reactions are much more common, and these may occur the first time an individual is exposed to a photosensitizing agent. These reactions are dose dependent, relying on both the amount of drug used and the amount of UVR the individual is exposed to<sup>9,15</sup>. In the phototoxic dermatitis, the photosensitizing agent, once activated by UVR, directly damages the tissue<sup>16</sup>. Usually, this reaction occurs minutes to hours after exposure to the agent and UVR. Clinically, it appears similar to sunburn and is restricted to the skin that has been exposed to sunlight<sup>10</sup>.

**Photoallergic reactions:** Photoallergic reactions only occur after an individual has already been sensitized to the agent and typically develop 24-72 h after exposure<sup>9,17</sup>. These occur through a cell-mediated immune response (type IV hypersensitivity reaction) that does not depend on the dose of drug or amount of UVR received. When the photosensitizer absorbs photons from UVR, the energized molecule can bind proteins in the skin and form new antigens<sup>18,19</sup>. These antigens are then processed by Langerhans cells and presented on the major histocompatibility complex (MHC) II to activate T-cells, which migrate to the skin to execute an immune response<sup>18</sup>. Photoallergic reactions manifest as eczematous, pruritic lesions, which may spread to involve other areas of the skin that were not previously exposed to the sun<sup>10,18</sup>.

### Ketoprofen

Ketoprofen, 3-(3-benzoylphenyl) propionic acid, is a NSAID that is known to cause photoallergic reactions. It exists in many preparations, including gels, creams, lotions, ointments, suppositories and oral medications<sup>18</sup>. Due to its anti-inflammatory effects and local analgesic properties, ketoprofen is often used for a variety of purposes, such as decreasing swelling, pain, fever and arthritis. There are several reports of photoallergic reactions due to ketoprofen use<sup>18</sup>. Despite being used less than other NSAIDs such as diclofenac and piketoprofen, ketoprofen remains one of the most frequent photoallergens<sup>18,20</sup>.

In this review, the clinical presentation of ketoprofen-induced photoallergic dermatitis and the possible mechanisms involved in its pathogenesis are discussed. The drugs with similar biochemical structures that cross-react with ketoprofen are summarized. Moreover, the management of

ketoprofen-associated photoallergic dermatitis is outlined.

### Ketoprofen-associated photoallergic dermatitis

**Clinical presentation:** Photoallergic dermatitis that occurs as a result of topical ketoprofen use presents acutely with erythema, oedema and papulovesicles on areas of skin exposed to both the drug and to sunlight (Figure)<sup>18,20,21</sup>. The lesions are often pruritic, and although these may initially appear only on sun-exposed areas, but may spread to involve other sites as well due to the systemic nature of the cell-mediated immune response<sup>18</sup>.

Other factors may also contribute to the spread of dermatitis, including transfer of the topical drug by hands or clothing to other body sites. In addition, ketoprofen may also contaminate clothing or shoes,



**Figure.** Distant (A) and closer (B) views of the right foot of a 62 yr old man who presented with ketoprofen-induced photoallergic dermatitis of the right three medial toes. He had chronic arthritic pain of the right great toe; the right second and third toes had more recently become painful after he had gone hiking and developed subungual haematomas of these toes and the left second toe. The patient applied ketoprofen gel to the medial three toes of the right foot to relieve pain and subsequently exposed them to sunlight while wearing sandals outside (C). Other areas of the body on which he applied ketoprofen gel but did not expose to sunlight did not develop dermatitis. Only the right three medial toes that were exposed to sunlight developed a photoallergic reaction. The patient was treated with triamcinolone 0.1 per cent cream and instructed to avoid oxybenzone sunscreen, and the redness and scaling resolved within one week.

which may lead to persistent dermatitis<sup>18</sup>. In some cases, patients who have previously been sensitized to ketoprofen may also develop systemic contact dermatitis when exposed to the drug through oral or parenteral administration. This may present as diffuse urticaria or as a generalized erythematous exanthem with maculopapular, vesicular or pustular features<sup>22</sup>.

**Pathogenesis:** Two models have been proposed to explain the creation of the photoallergen that induces the cell-mediated immune response<sup>23</sup>. The first called the photo-hapten model states that the photosensitizer and skin proteins initially co-exist in a non-covalent manner; once exposed to UVR, these bind covalently and form a hapten. In the second theory, termed the pro-hapten model, UVR first converts the photosensitizer into a hapten, which then binds to protein to form the photoallergen<sup>18</sup>.

Ketoprofen appears to function as a photo-hapten<sup>18</sup>, and some studies have proposed that the benzophenone moiety in ketoprofen is responsible for the drug's ability to cause photoallergy<sup>24,25</sup>. In addition, several other properties of ketoprofen appear to contribute to the development of photoallergic dermatitis. When irradiated, ketoprofen forms 3-ethyl-benzophenone as its main photoproduct, which is able to cause photo-peroxidation and red blood cell haemolysis<sup>18,26</sup>. Furthermore, DNA has been found to undergo single strand breaks in the presence of irradiated ketoprofen, and singlet oxygen formed from ketoprofen exposed to UVR can induce lipid peroxidation<sup>18,26,27</sup>. All of these factors may contribute to the development of photoallergic dermatitis.

**Interactions with other agents:** A variety of agents are known to aggravate or cross-react with ketoprofen-induced photoallergy. Ketoprofen is composed of a benzophenone moiety and propionic acid, and cross-reactions with agents that contain similar structures may occur. In particular, fenofibrate contains a benzophenone structure, and cross-photosensitization has been shown in photo-patch tests<sup>28</sup>. In addition, although the mechanism is unknown, photosensitization to ketoprofen appears to lead to photoallergic reactions to octocrylene, which is an agent widely used in sunscreens and cosmetics<sup>23,29</sup>.

**Management:** If ketoprofen-induced photoallergic dermatitis is suspected, photo-patch testing can confirm the diagnosis. Of note, as ketoprofen has anti-inflammatory properties, false negative or

delayed reactions may occur<sup>18</sup>. Therefore, postponing the reading of the patch test until 5-7 days after administration has also been suggested<sup>30</sup>. Usually, discontinuation of ketoprofen and avoidance of sun exposure, along with topical corticosteroid application, result in clinical improvement in about two weeks<sup>5</sup>. However, sometimes, there may be post-inflammatory hyperpigmentation, and rare cases of leukomelanoderma have been reported<sup>22</sup>.

## Conclusion

Ketoprofen-induced photosensitivity manifests as a photoallergic reaction, which occurs through a cell-mediated immune response. Specific structural features such as the benzophenone moiety appear to play a major role in ketoprofen's ability to induce photoallergy. In addition, these may be responsible for aggravation of the dermatitis and cross-reaction seen with other agents such as fenofibrate and octocrylene. Therefore, avoidance of these agents, either alone or in combination with ketoprofen, is recommended.

Use of topical or systemic corticosteroids, cessation of ketoprofen, sun protection and avoidance of known cross-reactive or exacerbating agents appear to be effective treatment methods for ketoprofen-induced photoallergy. As photoallergic dermatoses do not present immediately and may take a few days to appear, a high degree of clinical suspicion is necessary to make the correct diagnosis.

**Conflicts of Interest:** None.

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