Ketoprofen Allergic Reactions

Carmen Cantisani[1,*], Teresa Grieco[1], Valentina Faina[1], Carlo Mattozzi[1], Hanibal Bohnenberger[2], Emidio Silvestri[1] and Stefano Calvieri[1]

[1]*Department of Dermatology and Plastic Surgery, University Sapienza of Rome, vle del Policlinico 155, 00161; Rome, Italy,* [2]*Georg-August-University Robert-Koch-Straße 40 37075 Göttingen, Germany*

Received: July 13, 2009; Accepted: August 6, 2009; Revised: September 7, 2009

Abstract: Topical ketoprofen (KP) is widely used because of its anti-inflammatory effect. Parallel with its popular usage, the number of reported cases of ketoprofen-induced photoallergic contact dermatitis has increased. A review of the literature was made to evaluate the spectrum of cross sensitization in patients with ketoprofen-induced photoallergic contact dermatitis using ketoprofen and other structurally similar chemicals and sunscreens, fragrance components, as well as the presence of prolonged photosensitivity related to it. Furthermore, the distinction between true cross-reactivity and concomitant sensitization may be difficult. Therefore, further investigations are needed to gain a more complete understanding of this important topic. This article also reviews some patents related to alternative treatment of musculoskeletal diseases and/or treatment of allergic reactions due to NSAIDs use.

Keywords: Allergic contact dermatitis, benzophenones, cross-reactions, etofenamate, fragrances, ketoprofen, nonsteroidal anti-inflammatory agents, octocrylene, photopatch test series, photosensitivity.

INTRODUCTION

Ketoprofen [(KP); 2-(3-benzoylphenyl) propionic acid; Fig. (**1**)], an arylpropionic acid derivative (APAD), belongs to the group of nonsteroidal anti-inflammatory drugs (NSAIDs) [1]. It inhibits prostaglandin (PG) synthesis and is widely used to remove pain [2]. Oral ketoprofen was first sold by Rhone-Poulenc SA (Antony Cedex, France) in the late 1960s and only in 1977 in Japan. Topical medicament, containing 1% ketoprofen, was first sold by Farmitalia Carlo Erba (Italy) in 1972 while sector gel (containing 3% ketoprofen: Hisamitsu Pharmaceutical Co., Inc., Tosu, Japan) in 1986; although little evidence is available on the efficacy of the administration of non-steroidal anti-inflammatory drugs (NSAIDs) by topical route. Now, worldwide, many pharmaceutical preparations of ketoprofen are available, such as poultice, gel, tape, cream, lotions, ointment, oral medicine, injection suppositories, often without a medical prescription [3-5]. 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 photo allergic contact dermatitis from KP has been published, first from the Mediterranean countries and later also from more northern European areas and from Japan [1-11]. Contact allergy to topical ketoprofen (KP) is an emerging problem, whose diagnosis can be complex owing to the peculiar characteristics of NSAID and the possible inadequacy of current diagnostic methods, including concentration and vehicle used in patch testing. Skin symptoms are often severe and of long duration. While systemic photosensitization has been rarely reported, patients with photocontact dermatitis due to topical ketoprofen have been frequently reported [12]. The potentially misleading clinical features observed in some cases, the diversity of the casual substances identified, and low frequency with which photopatch testing is carried out in general, indicate that the occurrence of photoallergic contact dermatitis might be underestimated.

EPIDEMIOLOGY

Ketoprofen continues to be the most frequent photoallergen. Since the first case report in 1985 [4], and 44 cases of ketoprofen- induced photocontact dermatitis have been reported in the English literature. Females have been preferentially affected. Some countries, such as France, have modified the conditions of use for ketoprofen [8] because of the notification of a large number of photosensitivity reactions [9]. Therefore, as photosensitivity reactions are the most notorious for topical NSAIDs, it would seem important to determine the number of allergy cases and photo allergy, as well as their consumption, in order to verify the hypothesis that the number of cases is not directly related to use but that there are certain topical NSAIDs that are more allergenic. Usually the topical NSAID, which showed the most cases of allergy, was ketoprofen, however, it is not the most sold, it is used 79% less than diclofenac and 12% less than piketoprofen, medications responsible for only 2.1% and 3.6% of the contact reactions [13]. The extreme variability in the reported frequency of KP contact allergy might depend on the selection of patients evaluated in the case series, the methodology and the battery of NSAIDS used in patch testing, as well as their prescription patterns in different countries.

*Address correspondence to this author at the Department of Dermatology and Plastic Surgery. University Sapienza of Rome, Azienda Policlinico Umberto I, Via di Boccea n. 10 int. 16, 00167 Rome Italy;
Tel: +39-3479385719; Fax: +39-06490243;
E-mails: carmencantisanister@gmail.com; carmen.cantisani@uniroma1.it

1872-213X/10 $100.00+.00

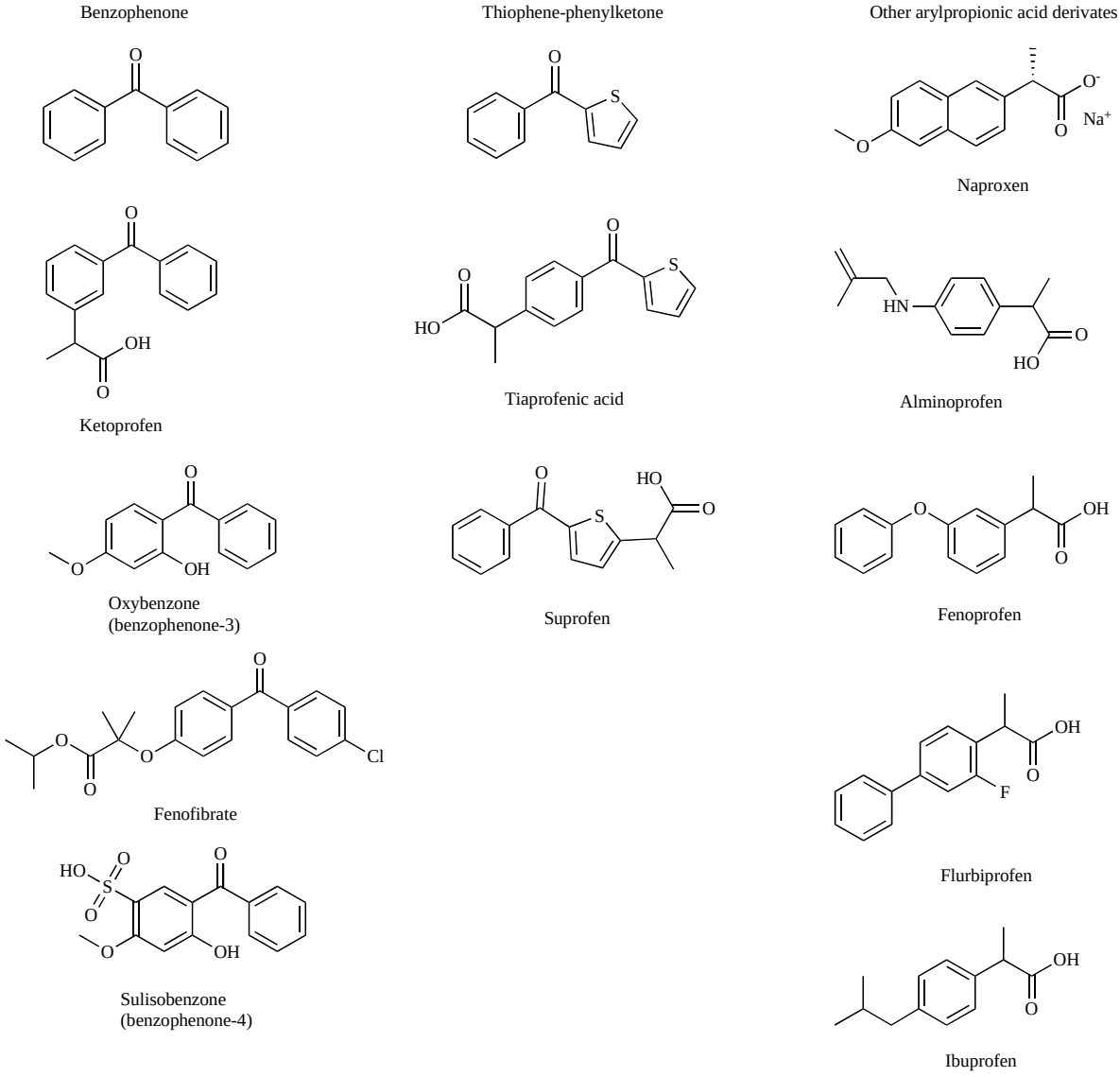

Fig. (1). Ketoprofen, suprofen and tiaprofenic acid are arylpropionic anti-inflammatories. Their chemical structures share the same elements as the benzoyl radical and the thiophene ring.

Clinical Features and Diagnostic Aspects

Photocontact dermatitis due to topical ketoprofen develops as an acute dermatitis with edema, erythema, papulovesicles Fig. (**2**), bullous Figs. (**3** & **4**), itching lesions or erythema exsudativum multiforme-like eruption Fig. (**5**) at the application site 1 week to 1 month after the initiation of use, depending on the frequency and intensity of sun exposure [8]. The lesions may be apparently confined to the body sites, such as elbows, knees, ankles, forearms, and thighs or several parts of the body may be affected where musculoskeletal problems and sun exposure concomitantly occur, but may also appear on other sites by transfer (ectopic contact dermatitis by hands or clothing; it may also affect family members due to connubial contact. Moreover, ketorpofen contaminates clothing, shoes, etc, explaining some of the persistent reactions [14]. Most of them presented with several types of skin lesions. Sometimes patients need systemic treatment with corticosteroids. Emergency visits in the hospital may occur. Cessation of the causative agents and avoidance of sun exposure in combination with topical application of glucocorticosteroids usually improve the symptoms in 2 weeks. However, residual post-inflammatory hyperpigmentation may occur, and in a rare instance, intractable leukomelanoderma has been reported in the Japanese literature [15]. In subjects previously sensitized to KP, the systemic absorption of these drugs through multiple routes of administration (oral, parenteral or topical) can induce the so-called systemic contact dermatitis, which can present as generalized macula-papular Fig. (**6**), papulo-vesicular, pustular or erythematous eruption as well as urticarial rash [15] Fig. (**7**).

Clinical suspicion should be confirmed by patch testing such as SIDAPA (Società Italiana di Dermatologia Allergologica Professionale ed Ambientale) patch test standard series, including fragrance mix and its components (eugenol, isoeugenol, oak moss, geraniol, hydroxycitronellal, amyl

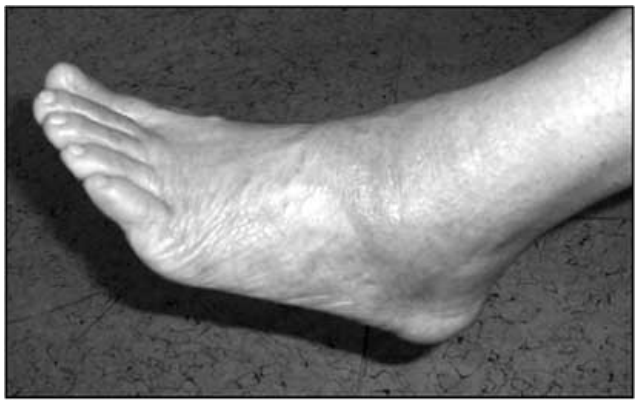

Fig. (2). Erythemato papulo-vesicular eruption.

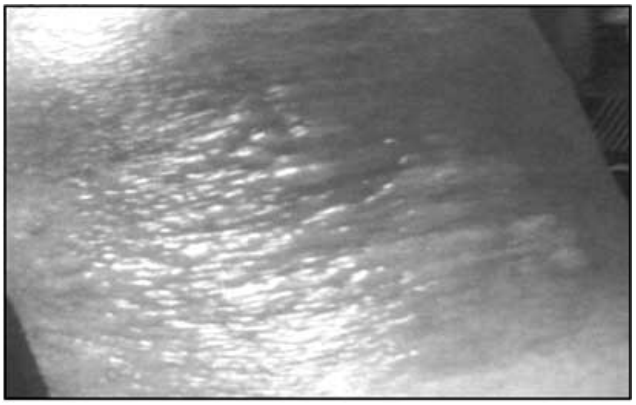

Fig. (3). Erythemato-bullous eruption.

Fig. (4). Patch by patch with topical ketoprofene showed a strong positivity with bullous eruption.

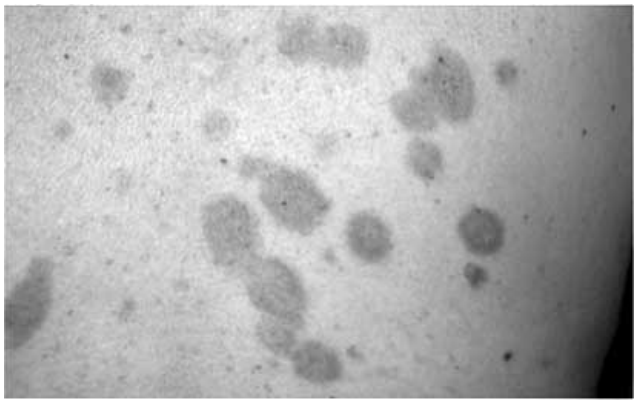

Fig. (5). Erythema exudativum multiforme-like eruption.

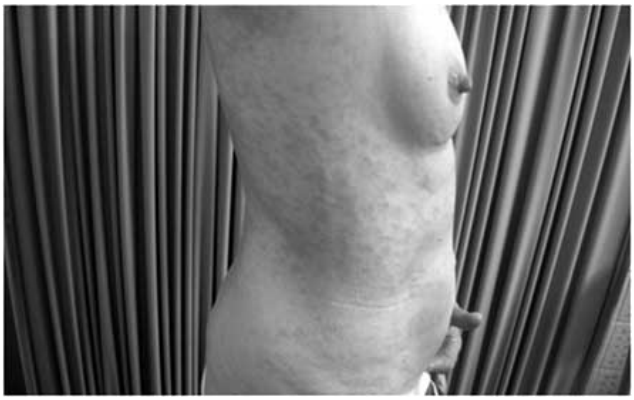

Fig. (6). Generalized macula-papular eruption.

Fig. (7). Urticarial rash.

cinnamaldehyde, cinnamyl alcohol and cinnamaldehyde) and with the SIDAPA photopatch test series**.** Patch tests with NSAIDs, in patients with contact sensitization to these agents, can evoke false negative reactions because of the intrinsic anti-inflammatory action of KP which may suppress or delay the cutaneous response. Therefore, reading should be postponed on day 5 or 7. At the first reading, the reaction may appear only at the edges of the test area, while it can be completely absent in its central portion, where the anti-inflammatory effect of KP is more evident because of the accumulation at higher concentrations. This phenomenon named “edge” or “border effect” fades away on successive readings after a few days [16] Fig. (**8**).

Fig. (8). The so called "border effect".

MECHANISMS UNDERLYING SENSITIZATION TO KPs

Photosensitization, phototoxicity or photoallergy is induced on exposure to sunlight after internal or external administration of ketoprofen [17]. Ketoprofen is absorbed via the gastrointestinal tract and is carried to the near surface of skin by the circulation where it is directly exposed to sunlight. In general, photoreactions by photosensitive chemicals are divided into the phototoxic and photoallergic types. While phototoxicity is mediated by active oxygen, especially singlet oxygen, photoallergy occurs as a consequence of a specific immune reaction mediated by antigen specific, sensitized T cells. This is clinically well known that KP induces photocontact dermatitis as an adverse reaction. KP has both phototoxic and photoallergic potentials, but many clinical observations have indicated that photosensitivity to KP is a photo allergic reaction [18-24]. In fact, ketoprofen *in vivo* tests, demonstrated relatively weak photo toxicity. Irradiation of ketoprofen in neutral aqueous solution resulted in the formation of 3-ethyl-benzophenone as the major photoproduct, and eight minor additional products. The major photoproduct elicits photoperoxidation, and causes red blood cell photohemolysis. Ketoprofen may induce DNA damage *in vitro* upon irradiation. DNA, in the presence of ketoprofen, undergoes single strand breaks involving hydroxyl radicals. Free radicals were reported to damage DNA and to induce hemolysis [15] and active oxygen species, superoxide anion and singlet oxygen generated from ultraviolet (UV)- exposed ketoprofen were found to contribute to dermatitis. The drug is able to induce photoperoxidation of linoleic acid in the photo-induced lipid peroxidation process. The two theories, named photo-hapten and pro-hapten models, have been put forward to explain the formation of photo-allergen [15]. According to the photo-hapten theory, photosensitizing chemicals and proteins need to coexist upon exposure to UVA in a non-covalent manner, and UVA turns it covalent [15-26]. On the other hand, the pro-hapten theory suggests that UVA simply converts photosensitizing substances into ordinary hapten, which subsequently binds with protein. It seems that most of photo-allergic substances have a photo-haptenic moiety; KP serves as a photo-hapten because of its photo-coupling ability to protein. Komamura proposed the importance of the benzoic ring and the ketone structure [27]. Coz concluded that the photoallergy is due to benzophenone moiety in ketoprofen or to a closely related thiophene-phenylketone part of the tiaprofenic acid rather than their arylpropionic acid function. Sugiura study concluded that the benzoyl radical, not benzophenone is the key structure for the photosensitization of KP suprofen and tiaprofenic acid and their photocross-reactivities [18-33] this contradiction is due to the limitation of the speculation from the clinical data. Patients had different personal histories using several kinds of drugs. They may have used the photo-reacted drugs independently which means there was the possibility of an independent photosensitization.

HISTOPATHOLOGICAL AND IMMUNOHISTO-CHEMICAL FEATURES

Photo-allergy is due to a cell-mediated hypersensitivity response, involving immunological reactions. Therefore, it only occurs in previously sensitized individuals and requires a latency period of sensitization.

Atarashi's [34] study suggested that photo-haptens bind to self-peptides located in the groove of major histo-compatibility complex (MHC) molecules of antigen-presenting cells. In photocontact dermatitis, epidermal Langerhans cells (LCs) serve as photo-antigen-presenting cells and transport a given photo-antigen to the draining lymph nodes where they present it to photo-antigen-specific T-cells [34]. Results suggest that KP plus UVA play an immuno-stimulatory role for these cells in the mouse strain which is highly responsive to KP photo treatment. KP plus UVA, but not KP or UVA alone, induces morphological changes of epidermal LCs and stimulates them to express MHC class II, CD86, CD80, CD54 and CD40 molecules, indicating that KP photo-treatment maturates LCs and the total applied amount of KP determines the response. Alternatively, some antigen-presenting cells other than LCs, such as dermal dendritic cells, might play a role for sensitization and elicitation of photo-contact dermatitis. Compared to ordinary contact hypersensitivity, however, UVA irradiation is required for sensitization, and therefore, dermal dendritic cells seem to be less photo-modified with KP than LCs. There are two possibilities in the reduction of LC number; one is that LCs undergoing maturation migrate to the draining lymph nodes, as previously documented in ordinary haptens. The other possibility remains that KP exerts phototoxic action to LCs. The phototoxic effect is minimal in this reduction, and the migration mechanism is more likely. Alternatively, KP possibly affects LC maturation by its pharmacological action of non-steroidal anti-inflammatory drug. Topical application of KP not only in the sensitizing but also non-sensitizing site suppressed CHS (contact hypersensitivity) response. The immune-suppression of CHS by topical application of KP is systemic and haptein-specific. T-reg cells play an important role in the suppressive effect of KP. It was in fact shown that KP inhibits the maturations of LCs inducing systemic and hapten-specific immunosup-pression systemically suppressing contact hypersensitivity via inducing T-reg cells [35,36], altering the function of antigen-presenting cells, or alternatively it might modulate T cells to become T-reg cells upon antigen-presentation. KP is not a classical cyclooxygenase inhibitor, but also LC down-modulator at a higher concentration, both the actions occur

even when KP is delivered via the skin and lead to the development of Treg cells [37].

Atarashi's [35] study suggests two clinically important notions. First, nonsteroidal anti-inflammatory drugs are capable of functioning as photo-hapten, thereby stimulating LCs to mature. Second, there are differences among individuals in the susceptibility of LC responses to photohaptenic drugs upon UVA exposure. A number of reports have documented patients with severe photo-contact dermatitis to KP [1-5]. In such cases, a predisposition to the photosensitivity might be closely associated with MHC haplotype [35].

CROSS - AND CONCOMITANT REACTIVITY

Many topical photo-allergic culprits have been reported in the literature, the most important of which are sunscreen agents and, recently, diuretic, antibacterial non-steroidal anti-inflammatory agents (NSAIDs) [38, 39]. Not at all exceptional is the occurrence of photo-aggravation and recurrent transient or even persistent light reactions previously exposed as well as non-exposed areas (often sparing the original application site), particularly with the NSAID ketoprofen. Moreover, cross-reactions with chemically-related as well as non-chemically related molecules are common. Photo sensitizing chemicals absorb ultraviolet (UV) and/or visible radiation, a characteristic that is essential for the chemical to be regarded as a photo-sensitizer. In order to elucidate the antigenic determinant in ketoprofen-induced photoallergy, studies on cross-reaction with structurally-related compounds are important. Ketoprofen is composed of a diphenylketone moiety (benzophenone) and propionic acid as a substitute. Cross-sensitivity reactions with other arylpropionic acid derivatives, such tiaprofenic acid, fenofibrate or oxybenzone-harboring benzoyl ketone or benzophenone may also occur.

According to the other ingredients in the ketoprofen-containing gels, some patients may react with a contact allergic reaction to other component in the gel, such as lavender oil which is a natural fragrance. Linalool, which is a major ingredient in lavender oil, is a sensitizer when oxidized [13]. Simultaneous contact allergy to fragrance mix and Myroxylon pereirae has been reported in patients photoallergic to ketoprofen [40-44]. Cinnamyl alcohol that is a component of both fragrance mix and Myroxylon pereirae has been suggested to explain this phenomenon [43]. As shown by Foti *et al.* in a computerized conformational analysis the structure of cinnamyl alcohol is similar to that of KP, whereas the structures of benzophenone-10, octocrylene and fenticlor are completely different. These results suggest that in patients with contact allergy to KP, 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.

DISCUSSION

The topical use of nonsteroidal anti-inflammatory drugs (NSAIDs), widely used for moderate acute and chronic painful conditions, is one of several strategies used to improve the tolerability profile of NSAIDs, particularly with regard to gastric and renal adverse effects. However, topical NSAIDs can induce photosensitivity. Among the different NSAIDs used topically, ketoprofen has often been implicated in photosensitivity reactions. The higher frequency of such adverse reactions with ketoprofen could be accounted for by its chemical structure and the variety of chemical reactions that give rise to phototoxic effects. In summary, ketoprofen is a potent photosensitizer with many simultaneous photocontact allergies to various photosensitizers, some of which have structural similarities. The widespread and repeated use of these agents may lead to sensitization, incurring a greater risk of systemic allergic reactions with oral NSAIDs or other drugs recognized to induce cross-reactions. Physicians and pharmacists should advise patients and inform them of the risks of topical NSAIDs which are often dispensed over the counter drugs. The interaction of sunlight with drug medication leads to photosensitivity responses in susceptible patients, and has the potential to increase the incidence of skin cancer. Adverse photosensitivity responses to drugs occur predominantly as a phototoxic reaction, which is more immediate than photoallergy, and can be reversed by withdrawal or substitution of the drug. The bias and inaccuracy of the reporting procedure for these adverse reactions are a consequence of the difficulty in distinguishing between sunburn and a mild drug photosensitivity reaction, together with the patient being able to control the incidence by taking protective action. Prevention of photosensitivity involves adequate protection from the sun with clothing and sunscreens. In concert with the preponderance of free radical mechanisms involving the photosensitizing drugs, some recent studies suggest that diet supplementation with antioxidants may be beneficial in increasing the minimum erythemal UV radiation dose. Patients with ketoprofen photo allergy should avoid using some NSAIDs, such as suprofen or tiaprofenic acid, and the antilipidemic. Quercetin works to suppress free radical and active oxygen species generation from the UV exposed ketoprofen, as well as to quench the free radicals. Consequently, quercetin has high potential for use as an excipient in ketoprofen ointments to suppress photo toxicity and photosensitization by ketoprofen.

The history is often not a good guidance to determine KP-related (photo) allergic contact dermatitis and the severe clinical symptoms sometimes require 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 photo patch testing with KP might be indicated. We concluded that topical medicaments containing ketoprofen should not be used on exposed areas during spring and summer.

CURRENT & FUTURE DEVELOPMENTS

The pathogenesis of a wide variety of local disorders (e.g. skin, joints, muscle, and ligaments) involves an inflammatory process. While a range of treatments have been developed for local inflammatory conditions, none are completely effective or free of adverse side effects. Treatments for different inflammatory skin conditions typically include topical or oral steroids, ultraviolet light, antibiotics, and other anti-inflammatory therapies. Many undesirable side effects are usually seen, there are now a variety of newer drugs

available to prevent or treat them. New compositions have been discovered that when topically applied, deliver therapeutic levels of an agent with anti-inflammatory activity to the local targets in an individual with a local inflammatory disorder Topical compositions are useful for delivering a therapeutic level of an NSAID to a target within a subject having a local inflammatory disorder. It has been discovered that it has one or more advantageous pharmacodynamic, pharmacokinetic, and/or therapeutic properties and provide therapeutic levels of NSAID for a diverse range of local inflammatory disorders [45]. Moreover, therapeutic levels of an NSAID are attained with minimal systemic delivery using low alkanol compositions.

Another invention for treating or preventing either of inflammatory disease or allergic reactions provides compounds of leukotriene biosynthesis inhibitors [46, 47].

One recent patent application describes a class of 9 substituted-8- oxoadenine compounds having immunomodulating properties which act via TLR7 that are useful in the treatment of allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyperresponsiveness; delayed-type hypersensitivity reactions and in the treatment of the inflammatory diseases COPD, asthma and allergic rhinitis the compounds of the invention may be combined with inhibitors whether applied topically or systemically[48]. None of the previous reported patents is completely free from adverse reactions so a patent able to prevent or reduce a photosensitivity and/or phototoxicity reaction which may be caused by a once-per-day dose of an over-the-counter or prescription medication which causes a photosensitivity and/or phototoxicity reaction in a human or animal should be useful [49]. The vast majority of drugs that could be delivered through the skin are unable to be approved by regulatory bodies due to safety issues concerning their skin irritation and or skin sensitization. A relatively new invention concerns a method for the elimination of adverse skin reactions due to the use of skin irritating and skin sensitizing transdermally and topically administered drugs and/or delivery system components, whether through continuous or pulsatile delivery; and the delivery systems constructed utilizing the method. Also disclose new, anti-irritant uses of compounds, providing prophylactic and therapeutic treatment of transdermal and topical drug-induced contact dermatitis. Topical drug delivery systems may be used to treat, prevent, eliminate, reduce, inhibit or modulate adverse skin reactions [50].

In conclusion, although cross-reaction phenomena among NSAIDs have been thoroughly studied and defined, further investigations are warranted to gain a more complete understanding of this problem.

ACKNOWLEDGMENTS

We would like to thank Dr. U. D'Ambrosio,V. Cantisani, A. Marcantonio, Dr. L. Melis, Policlinico Umberto I of Rome, Italy, Dr. D.M. Miller, Harvard Medical School Boston, Massachusetts for their technical and linguistic assistance and Mrs. Sonia Tofani for her collaboration.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

REFERENCES

[1] Curry SL, Cogar SM, Cook JL. Nonsteroidal anti-inflammatory drugs: A review. J Am Anim Hosp Assoc 2005; 41(5): 298-309.
[2] Kantor TG. Ketoprofen: A review of its pharmacologic and clinical properties. Pharmacotherapy 1986; 6(3): 93-103.
[3] Clark JO, Clark TP. Analgesia. Vet Clin North Am Equine Pract 1999; 15(3): 705-723.
[4] Milpied-Homsi B. Allergies to ketoprofen gels. Presse Med 2001; 30(12): 605-609.
[5] Alomar A. Ketoprofen photodermatitis. Contact Dermatitis 1985; 12: 112-113.
[6] 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.
[7] Valsecchi R, Falgheri G, Cainelli T. Contact dermatitis from ketoprofen. Contact Dermatitis 1983; 9: 163-164.
[8] Veys EM. 20 years' experience with ketoprofen. Scand J Rheumatol 1991; 90 (Suppl): 1-44.
[9] Veyrac G, Paulin M, Milpied B, Bourin M, Jolliet P. Results of a French nationwide survey of cutaneous side effects of ketoprofen gel reported between September 1996 and August 2000. Therapie 2002; 57(1): 55-64.
[10] Avouac B, Teule M. Ketoprofen: The European experience. J Clin Pharmacol 1988; 28(12 Suppl): S2-7.
[11] Matthieu L, Meuleman L, Van Hecke E, *et al*. Contact and photocontact allergy to ketoprofen. The Belgian experience. Contact Dermatitis 2004; 50: 238-241.
[12] Alomar A. Ketoprofen photodermatitis. Contact Dermatitis 1985; 12: 112-113.
[13] Diaz RL, Gardeazabal J, Manrique P, *et al*. Greater allergenicity of topical ketoprofen in contact dermatitis confirmed by use. Contact Dermatitis 2006; 54(5): 239-243.
[14] Hindsén 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(2): 215-219.
[15] Sugiura M, Hayakawa R, Xie Z, Sugiura K, Hiramoto K, Shamoto M. Experimental study on phototoxicity and the photosensitization potential of ketoprofen, suprofen, tiaprofenic acid and benzophenone and the photocross-reactivity in guinea pigs. Photodermatol Photoimmunol Photomed 2002; 18: 82-89.
[16] Gebhardt M, Wollina U. Cutaneous side-effects of nonsteroidal anti-inflammatory drugs (NSAID). Rheumatology 1995; 54(6): 405-412.
[17] Horn HM, Humphreys F, Aldridge RD. Contact dermatitis and prolonged photosensitivity induced by ketoprofen and associated with sensitivity to benzophenone-3. Contact Dermatitis 1998; 38: 353-354.
[18] Matsushita T, Kamide R. Five cases of photocontact dermatitis due to topical ketoprofen: Photopatch testing and cross-reaction study. Photodermatol Photoimmunol Photomed 2001; 17(1): 26-31.
[19] Le Coz CJ, Bottlaender A, Scrivener JN, *et al*. Photocontact dermatitis from ketoprofen and tiaprofenic acid: Cross-reactivity study in 12 consecutive patients. Contact Dermatitis 1998; 38: 245-252.
[20] Alomar A. Ketoprofen photodermatitis. Contact Dermatitis 1985; 12: 112-113.
[21] Bagheri H, Lhiaubet V, Montastruc JL, Chouini-Lalanne N. Photosensitivity to ketoprofen: Mechanisms and pharmacoepidemiological data. Drug Saf 2000; 22(5): 339-349.
[22] Ohtsu A. Mechanism of ketoprofen photosensitivity. Rinsho Derma 1990; 32: 1039-1046.
[23] Przybilla B, Schwab-Przybilla U, Ruzicka T, Ring J. Phototoxicity of non-steroidal anti-inflammatory drugs demonstrated *in vitro* by a photo-basophil-histamine-release test. Photodermatology 1987; 4: 73-78.

[24] Mozzanica N, Pigatto P. Contact and photocontact allergy to ketoprofen: Clinical and experimental study. Contact Dermatitis 1990; 23: 336-340.
[25] Sugiyama M, Nakada T, Hosaka H, Sueki H, Iijima M. Photocontact dermatitis to ketoprofen. Am J Contact Dermatitis 2001; 12: 180-181.
[26] Kurumaji Y, Ohshiro Y, Miyamoto C, Keong CH, Katoh T, Nishioka K. Allergic photocontact dermatitis due to suprofen. Photopatch testing and cross-reaction study. Contact Dermatitis 1991; 25: 218-223.
[27] Komamura H, Adachi J, Tani M, Yoshikawa K. Two cases of photocontact dermatitis due to suprofen. Environ Dermatol 1997; 4: 297-303.
[28] Bagheri H, Lhiaubet V, Montastruc JL, Chouini-Lalanne N. Photosensitivity to ketoprofen. Mechanisms and pharmaco-epidemiological data. Drug Saf 2000; 22: 339-349.
[29] Serrano G, Fortea JM, Latasa JM, *et al*. Photosensitivity induced by fibric acid derivatives and its relation to photocontact dermatitis to ketoprofen. J Am Acad Dermatol 1992; 27(2 Pt 1): 204-208.
[30] Durbize E, Vigan M, Puzenat E, *et al*. Spectrum of crossphotosensitization in 18 concecutive patients with contact photoallergy to ketoprofen: Associated photoallergies to non-benzophenone-containing molecules. Contact Dermatitis 2003; 48: 144-149.
[31] Leroy D, Dompmartin A, Szczurko C, Michel M, Louvet S. Photodermatitis from ketoprofen with cross-reactivity to fenofibrate and benzophenones. Photodermatol Photoimmunol Photomed 1997; 13: 93-97.
[32] Coz CJL, Bottlaender A, Scrivener JN, *et al*. Photo contact dermatitis from ketoprofen and tiaprofenic acid: Cross-reactivity study in 12 consecutive patients. Contact Dermatitis 1998; 38: 245-252.
[33] Le Coz C J, Bottlaender A, Scrivener J-N, *et al*. Photocontact dermatitis from ketoprofen and tiaprofenic acid: Cross-reactivity study in 12 consecutive patients. Contact Dermatitis 1998; 38: 245-252.
[34] Atarashi K, Kabashima K, Akiyama K, Tokura Y. Stimulation of Langerhans cells with ketoprofen plus UVA in murine photocontact dermatitis to ketoprofen. J Dermatol Sci 2007; 47: 151-159.
[35] Atarashi K, Mori T, Ryutaro Y, Kabashima K, Kuma H, Tokura Y. Skin application of ketoprofen systemically suppresses contact hypersensitivity by inducing CD4+CD25+ regulatory T cells. J Dermatol Sci 2009; 53: 216-221.
[36] de la Cuadra-Oyanguren J, Pérez-Ferriols A, Lecha-Carrelero M, *et al*. Results and assessment of photopatch testing in Spain: Towards a new standard set of photoallergens. Actas Dermosifiliogr 2007; 98(2): 96-101.
[37] Atarashi K, Kabashima K, Akiyama K, Tokura Y. Skin application of the nonsteroidal anti-inflammatory drug ketoprofen downmodulates the antigen-presenting ability of Langerhans cells in mice. Br J Dermatol 2008; 159(2): 306-313.
[38] Pigatto PD, Mozzanica N, Bigardi AS, *et al.* Topical NSAID allergic contact dermatitis. Italian experience. Contact Dermatitis 1993; 29(1): 39-41.
[39] Przybilla B, Ring J, Schwab U, Galosi A, Dorn M, Braun-Falco O. Photosensitizing properties of nonsteroidal antirheumatic drugs in the photopatch test. (In German). Hautarzt 1987; 38: 18-25.
[40] Pigatto P, Bigardi A, Legori A, Valsecchi R, Picardo M. Cross-reactions in patch testing and photopatch testing with ketoprofen, thiaprophenic acid and cinnamic aldehyde. Am J Contact Dermatitis 1996; 7: 220-223.
[41] Matura M, Skold M, Borje A, *et al*. Selected oxidized fragrance terpenes are common contact allergens. Contact Dermatitis 2005; 52: 320-328.
[42] Hausen BM, Simatupang T, Bruhn G, Evers P, Koenig WA. Identification of new allergenic constituents and proof of evidence for coniferyl benzoate in Balsam of Peru. Am J Contact Dermatitis 1995; 6: 199-208.
[43] Girardin P, Vigan M, Humbert P, Aubin F. Cross-reactions in patch testing with ketoprofen, fragrance mix and cinnamic derivatives. Contact Dermatitis 2006; 55(2): 126-128.
[44] Hughes TM, Stone NM. Benzophenone 4: An emerging allergen in cosmetics and toiletries? Contact Dermatitis 2007; 56: 153-156.
[45] Spann-Wade, M., Fedde, K.N.: US20080317684 (**2008**).
[46] Blouin, M., Grimm, E. L., Gareau, Y., Gagnon, M., Juteau, H., Laliberte, S., Mackay, B., Friesen, R.: US20090030048 (**2008**).
[47] Ducharme, Y., Yao-Hsiang W.T., Frenette, R.: US20090054483 (**2009**).
[48] Abbot, P., Bonnert, R. V., Brough, S., Chohan, K., McInally, T., Thom, S., Isobe, Y., Nakamura, K., Tojo, S.: US20090082332 (**2009**).
[49] Klimstra, P. D., Roniker, B., Swabb, E. A.: US5668134 (**1997**).
[50] Wille, J.J.: US2007042026A1 (**2007**).