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Photosensitivity to Ketoprofen
Mechanisms and Pharmacoepidemiological Data

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Contents

Abstract

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. Photosensitivity includes both phototoxic and photoallergic reactions.

Phototoxicity can be studied in the cell system and on biological targets such as cellular membranes or DNA. In hepatocyte cultures, data suggest that radical intermediates play a role in ketoprofen-photosensitised damage by cell membrane lysis. Photosensitised lysis of red blood cells has been employed as an indicator of membrane damage. Ketoprofen irradiation promotes the photolysis of erythrocyte suspensions. The drug is able to induce photoperoxidation of linoleic acid in the photo-induced lipid peroxidation process. The results obtained from the addition of radical scavengers suggest the involvement of free radicals in these processes.

Ketoprofen may induce DNA damage *in vitro* upon irradiation. DNA, in the

presence of ketoprofen, undergoes single strand breaks involving hydroxyl radicals as evidenced by the use of scavengers. Simultaneously with single strand breaks, pyrimidine dimers are formed by an energy transfer mechanism. The oxygen-dependence of both processes suggest competition between a radical process leading to DNA cleavage and a poorly efficient energy transfer between ketoprofen and pyrimidines at the origin of the dimerisation process.

Photoallergy is due to a cell-mediated hypersensitivity response involving immunological reactions. Therefore, it only occurs in previously sensitised individuals and requires a latency period of sensitisation. Among NSAIDs, ketoprofen is the main drug involved in this photoallergic contact dermatitis. Cross-sensitivity reactions with other arylpropionic acid derivatives, such tiaprofenic acid, fenofibrate or oxybenzone-harbouring benzoyl ketone or benzophenone may also occur.

Finally, 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. The widespread and repeated use of these agents may lead to sensitisation, incurring a greater risk of systemic allergic reactions with oral NSAIDs or other drugs recognised to induce cross-reactions. Physicians and pharmacists should advise patients and inform them of the risks of topical NSAIDs which are often dispensed as over the counter drugs.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in the treatment of pain and inflammatory conditions, and account for around 5% of all National Health Service prescriptions in Great Britain.[1] In 1994, pharmacies in the US dispensed over 68 million prescriptions for NSAIDs.[2] However, their use is restricted by the high incidence of adverse effects, particularly in the gastrointestinal tract and kidneys. Gastrointestinal damage includes multiple small lesions, gastric and duodenal ulcers, perforated ulcers, and severe bleeding of the upper gastrointestinal tract. The attributable risk of hospitalisation because of NSAID-induced gastric damage is 1.3 to 1.6% annually for regular users.[3] In an attempt to improve the tolerability profile of NSAIDs, a number of experimental and clinical studies have been carried out on selective cyclo-oxygenase (COX)-2 inhibitors. The data collected by the North American database, the American Rheumatism Association Medical Information System (ARAMIS) found significant differences in the occurrence of serious gastrointestinal effects requiring hospitalisation between 16 NSAIDs.[4] Other strategies involve coadministration of gastroprotective agents or modification of delivery systems.[5] Topical NSAIDs are widely used for moderate acute and chronic painful conditions and are available without prescription.[6]

It is also recognised that NSAIDs induce photosensitivity,[7] defined as exaggerated or abnormal cutaneous reactions to light. This adverse reaction seems to be reported more commonly with topical formulations, which may be because of the higher concentrations of NSAIDs in the skin. Among the different topical formulations of NSAIDs, ketoprofen has often been associated with photosensitivity reactions.[8-10] This propionic acid derivative is used in the treatment of musculoskeletal and joint disorders, ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, as well as in periarticular disorders such as tendinitis and in mild to moderate pain and other inflammatory conditions. It is currently used orally, rectally, intramuscularly or intravenously as the sodium salt. Ketoprofen can also be applied topically as a 2.5% gel for local pain relief. Only a small amount of ketoprofen is absorbed following topical application.[11] It has been reported that photosensitivity induced by keto-

profen may lead to hospitalisation in 1 out of 10 cases.[12]

Photosensitivity includes both phototoxic and photoallergic reactions. We review here the *in vitro* photosensitivity effects of ketoprofen which may help comprehend the high incidence and seriousness of the clinical reports.

1. Phototoxicity

Phototoxicity is dependant on the direct absorption of light energy. It can occur in anybody exposed to enough light energy in the presence of photosensitisers in the skin. Drugs, either absorbed locally into the skin or via the systemic circulation, may be the object of photochemical reactions within the skin. This can lead directly to chemically-induced photosensitivity reactions or to an enhancement of the usual effects of sunlight. Cutaneous reactions including erythema, oedema, bulla, desquamation or hyperpigmentation may occur within minutes of the first exposure or they may develop later (about 20 hours). Such reactions regress on discontinuation of drug administration or exposure to light.

Drug-induced phototoxicity can be associated with the formation of toxic photoproducts or the generation of short-lived intermediates such as free radicals which interact with biological substrates. Several approaches can be employed to determine the origin of the phototoxicity. Phototoxicity can be studied in the cell system, and also in specific targets such as cellular membranes or DNA.

1.1 Cell Cultures

Irradiation of the suspect drug incorporated into cells has been used for *in vitro* study of its phototoxicity. The various tests used depend on the nature of the cell. For example, phototoxicity can be evaluated by measuring depletion of the intracellular activity of lactate dehydrogenase from rat hepatocytes or fibroblasts in culture. From the dose-response curve, the concentration which leads to 10% of the maximal toxic effect could be estimated.[13] The reaction mixtures obtained on irradiation of ketoprofen are toxic to rat hepatocyte cultures. This effect is quantitatively more important when irradiation is carried out under aerobic conditions, indicative of a higher toxicity of oxygenated photoproducts.[13] The phototoxicity of ketoprofen occurs at lower concentrations (10^{-3} to 10^{-4} mol/L) than those found in the skin. These data suggest that phototoxicity probably results from the production of short-lived intermediate products such as free radicals rather than from toxic photoproducts.[13]

Since the survival of such chemical entities in the photomixtures would be expected to be extremely short, their effects can be evaluated by simultaneous irradiation of the drug in the presence of rat hepatocytes or fibroblasts. The results obtained by simultaneous co-irradiations of ketoprofen with hepatocyte suspensions indicated that radical intermediates play a role in ketoprofen-photosensitised damage by cell membrane lysis.

Furthermore, the phototoxicity of ketoprofen could also be confirmed by *in vitro* studies on leucocyte damage evaluated by monitoring the release of histamine from cells in suspension.[14]

1.2 Photohaemolysis

Photosensitised lysis of red blood cells has been employed as an indicator of membrane damage. Ketoprofen irradiation promotes the photolysis of erythrocyte suspensions. The concentration range of ketoprofen-inducing photohaemolysis *in vitro* can be found in blood after the administration of clinically relevant doses of ketoprofen.[9,13,15] The percentage of membrane lysis is higher than 90% after 1 hour of irradiation in the presence of ketoprofen at concentrations of 3×10^{-5} mol/L. The membrane damage induced by this photohaemolysis was found to take place by both oxygen-dependent and oxygen-independent mechanisms.[15] The addition of radical scavengers such as reduced glutathione, superoxide anion scavengers such as superoxide dismutase, and hydroxyl radical scavengers (e.g. mannitol) was found to significantly decrease photohaemolytic reactions, suggesting the involvement of free radicals in this process.[13,15] Taken together, these data indicate that

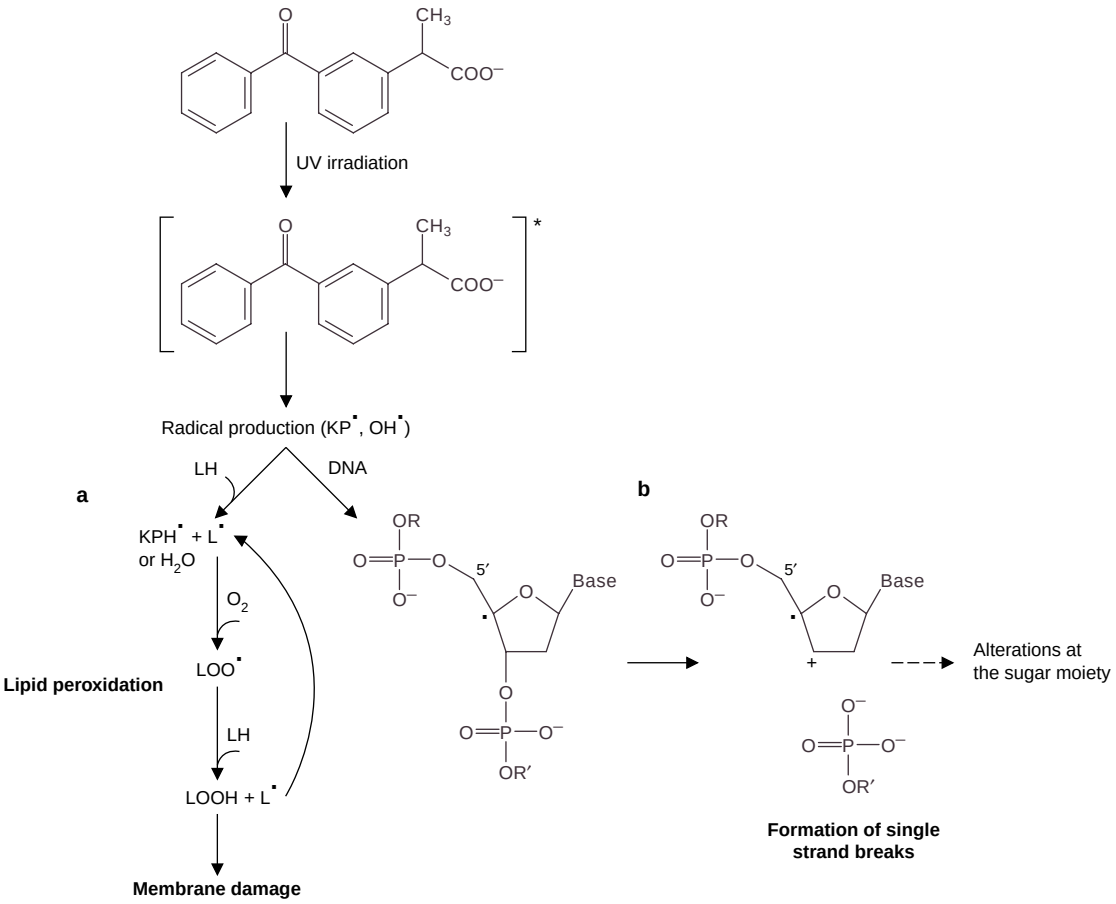

Fig. 1. General scheme of lipid peroxidation (**a**) and single strand breaks photosensitised by ketoprofen (**b**). **KP** = ketoprofen; **L•** = lipid radical; **LH** = unsaturated lipid; **LOOH** = lipid-derived dienic hydroperoxide; **UV** = ultraviolet; **[ ]*** = excited state.

much of the phototoxicity of ketoprofen stems from photosensitised damage of cell membranes via radical intermediates.

1.3 Photo-Induced Lipid Peroxidation

Aerobic cells are regularly exposed to the potential damaging effects of oxidants. One of the most important examples of such damage is lipid peroxidation, following oxidative degradation of phospholipids, cholesterol and other unsaturated lipids (fig 1a). Lipid peroxidation, which is highly detrimental to cell membrane structure and function, 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.

Ketoprofen is able to induce photoperoxidation of linoleic acid.[13,16] In the presence of drug concentrations of 10^{-5} mol/L, irradiation of linoleic acid induced the formation of a significant amount of dienic hydroperoxide characterised by the appearance of a new absorption band at 233nm. The decrease of dienic hydroperoxide levels after the addition of radical scavengers supports the role of

radical intermediates in the photo-induced lipid peroxidation process. However, the singlet oxygen quencher 1,4-diazabicyclol octane did not induce significant inhibition of peroxidation.[2] This shows that the oxygen excited state (singlet state) is not involved.

1.4 DNA Damage

Several studies have demonstrated that DNA bases can absorb in the ultraviolet (UV) spectrum, especially between 220 and 320nm (UVC and UVB).[17] Thus, cell death or mutation after UVC or UVB irradiation may follow UV absorption by cellular DNA. This direct photon absorption by DNA leads to the production of various photoproducts: pyrimidine dimers, which are recognised aetiological agents in skin cancer; and (6-4)-pyrimidine adducts (fig 2). However, the formation of DNA single strand breaks was relatively low. The induction of single strand breaks may be a combination of frank breaks and an alteration of alkali-labile sites giving rise to modified bases and abasic lesions. On the other hand, DNA damage can also result from absorption of photons by other molecular structures and photosensitisers, which then transfer energy to the bases of DNA. Figure 3 illustrates the mechanism of formation of pyrimidine dimers by energy transfer.

Ketoprofen at a concentration of 10^{-4} mol/L may induce DNA damage *in vitro* upon irradiation and photosensitise the formation of pyrimidine dimers and single strand breaks[18] with a quantum yield of 2×10^{-4} and 5×10^{-4}, respectively. Both kinds of damage were assessed by agarose gel electrophoresis analysis of DNA-ketoprofen mixtures irradiated at 313nm. The results were compared with those induced by acetophenone (a well known photosensitiser of thymine dimerisation), at the same concentration. On irradiation of DNA alone at 313nm, pyrimidine dimers were observed, while single strand breaks were not detected. DNA, in the presence of ketoprofen, undergoes single strand breaks involving hydroxyl radicals (fig 1b) as evidenced by the use of specific scavengers. An electron transfer process like that observed with benzophenone was also suspected.[18-21] Under aerobic conditions, ketoprofen photo-induced cleavage of DNA was predominantly a photodimerisation producing pyrimidine dimers, whereas under anaerobic conditions, less cleavage was observed in favour of dimerisation.

These findings are indicative of competition between a radical process leading to DNA cleavage and a low efficiency energy transfer between ketoprofen and the pyrimidines at the origin of the dimerisation process. This is the first *in vitro* example of a phototoxic drug generating cyclobutylpyrimidine dimers in DNA. This behaviour may be related to a substituted benzophenone, which is able to induce both electron and energy transfer to DNA.[21] Similar experiences have been observed with other NSAIDs. The findings indicate that the extent of DNA damage due to NSAID photosensitisation depends on the structure of the drug and the kind of damage involved. Among the different NSAIDs, only ketoprofen and tiaprofenic acid (both harbouring arylpropionic acid structures) promote the 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 dangerous.[18]

1.5 Photolysis

Ketoprofen is frequently administered as a gel ointment by topical application. Since the drug is exposed directly to light, its photochemical reactivity is very important.

On irradiation in aqueous buffer solution, ketoprofen undergoes a decarboxylation process, producing radical derivatives and photoproducts which damage DNA and have lytic activity on cells. Spectroscopic studies have indicated that the main product formed under aerobic conditions is 3-benzoylphenylethane.[15,16] In fact, photodecarboxylation of ketoprofen proceeds by 2 pathways: formation of a benzylic radical and benzylic carbanion (fig 4).[16,22,23] In the first pathway, ketoprofen in the excited state (a), undergoes a photoionisation with ejection of an electron and formation

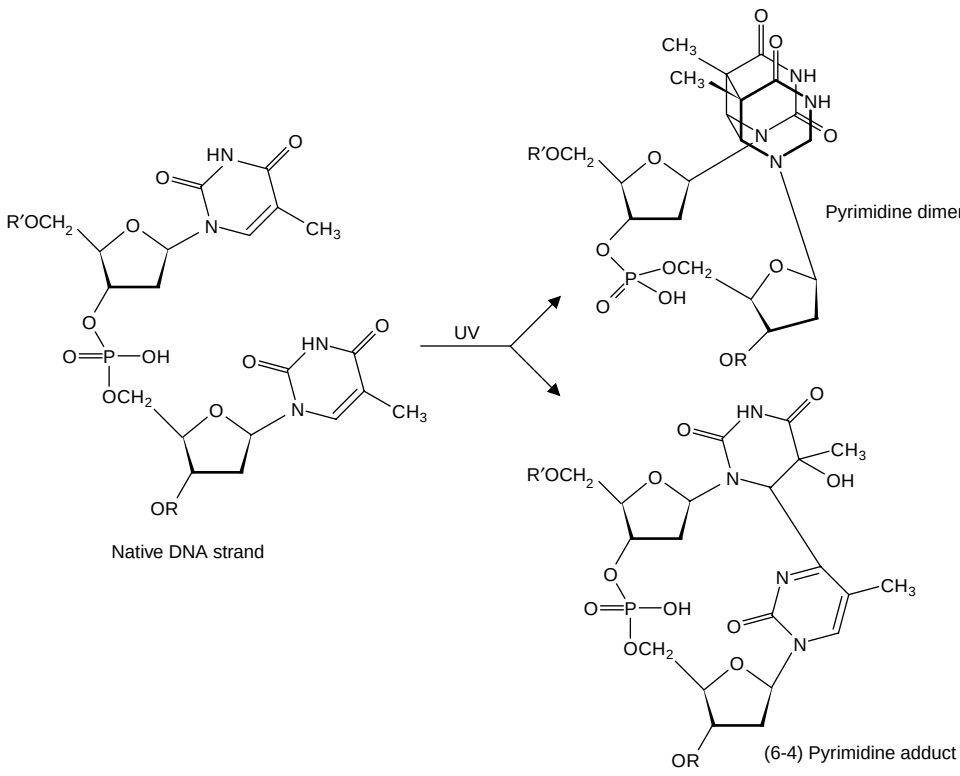

Fig. 2. Structure of pyrimidine photoproducts. **UV** = ultraviolet irradiation.

of a free radical, followed by loss of CO_2 and generation of a benzylic radical (b). This pathway is relatively minor. In contrast, the major pathway leads to an electron transfer between the carboxyl (donor) and the carbonyl (acceptor) generating a biradical triplet (c). After the loss of CO_2, a benzylic carbanion is generated, which would be expected to undergo a protonation finally leading to the formation of 3-benzoylphenylethane (d).[22] It should perhaps be noted that the minor pathway is less efficient at low light levels, but may become important with high light intensities.[22]

2. Photoallergy

Photoallergy is a delayed T cell–mediated hypersensitivity response involving immunological reactions. It occurs following topical exposure to drugs and is also characterised by possible ectopic cutaneous responses and generalised reactions following systemic administration of the incriminating drug. It requires a previous sensitisation and a latency period. After light irradiation, cutaneous reactions appear around 24 hours after drug rechallenge. Lesions are polymorph and eczematiform. Contrary to phototoxicity, lesions may extend to nonirradiated areas, and the reactions are dose-independent. The regression of cutaneous symptoms after drug withdrawal may take several months.[24]

Patch testing has been used extensively for the diagnosis of contact allergy and to confirm sensitivity in patients with delayed-type reactions.[25] It consists of the application of the suspect agent (hapten) on the skin with occlusive dressing and the subsequent reading of dermatological reactions

(after 24h, 48h or more). The photopatch test can also be used to confirm the diagnosis of photoallergic reactions. This test must reproduce a photosensitisation reaction after application of the suspect agent on the skin under a defined spectrum of irradiation.

Among NSAIDs, ketoprofen is the main drug involved in photoallergic contact dermatitis, although the molecular basis of ketoprofen-induced photoallergy remains to be fully elucidated. Since 1989, several cases of this adverse reaction have been reported with ketoprofen, particularly in mediterranean countries like Spain or Italy with high sun exposure.[26] On irradiation (particularly UVA), the photosensitiser is transformed to a hapten involving the benzophenone moiety, which leads to an immune response after binding to a tissue antigen. Rechallenge with this agent with optimal wavelengths stimulates the immunological reaction. The photoallergic reactions usually regress within some weeks after discontinuation of the drug. The photosensitising potential of ketoprofen occurs mainly in the UVA spectrum, although the UVB spectrum can not be totally excluded.[26]

Cross-sensitivity reactions may occur with other arylpropionic acid derivatives such tiaprofenic acid. A study involving different NSAIDs in 123 patients showed frequent cross-reactivity of ketoprofen with tiaprofenic acid.[27] Cross-sensitivity reactions may also be observed with different chemical families such fenofibrate or oxybenzones harbouring a benzoyl ketone or benzophenone moiety. Other authors have reported positive cross-reactions with ketoprofen in patients treated with fenofibrate.[24,28] Table I summarises ketoprofen-induced photocontact dermatitis case reports after application of topical ketoprofen gel 2.5% with photopatch testing or cross-sensitivity reaction investigations.

3. Epidemiological Data

With the exception of case reports of NSAIDs or ketoprofen-induced photosensitisation, epidemiological data are lacking. In order to assess cutaneous adverse reactions attributable to systemic or topical NSAID and antibacterial administration, a prospective epidemiological survey was carried out over 4 months in 1988 to 1989 by the Italian Group for Epidemiological Research in Dermatology.[40] NSAIDs were implicated in 49.3% of cases out of a total of 1457 case reports. Among them, ketoprofen was associated with 8.2% of the cases after aminophenazone (21.3%) and aspirin (acetylsalicylic acid) [11.3%]. However, photosensitisation was not explicit in the data.

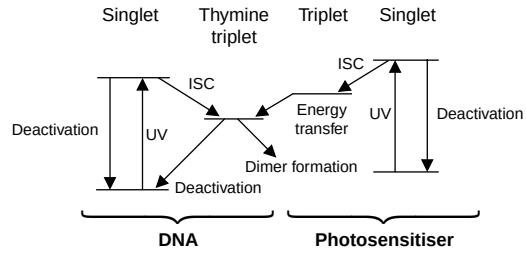

Fig. 3. Mechanism of formation of pyrimidine dimers by energy transfer. **UV** = UV irradiation; **ISC** = intersystem crossing.

Since their introduction in France in 1989, ketoprofen gels have been responsible for various cutaneous adverse effects, essentially photosensitisation and photocontact dermatitis. A study conducted by the French Drug Surveillance System[12] identified 337 cases of cutaneous adverse events associated with the commercial gel with a frequency ranging from 0.008 to 0.023%. The gender ratio was well distributed. There was clearly a predominance of young (30 to 40 years) and athletic individuals. Adverse reactions were severe in 40% of the cases. Factors associated with adverse effects were essentially exposure to the sun (31.5% of the cases) and occlusive dressing (13.8% of the cases). No predisposing conditions were noted, although 2.6% and 8.5%, respectively, involved earlier sensitisation by topical NSAIDs. The photopatch test (conducted in only 5 patients) was positive for ketoprofen in all 5 patients.

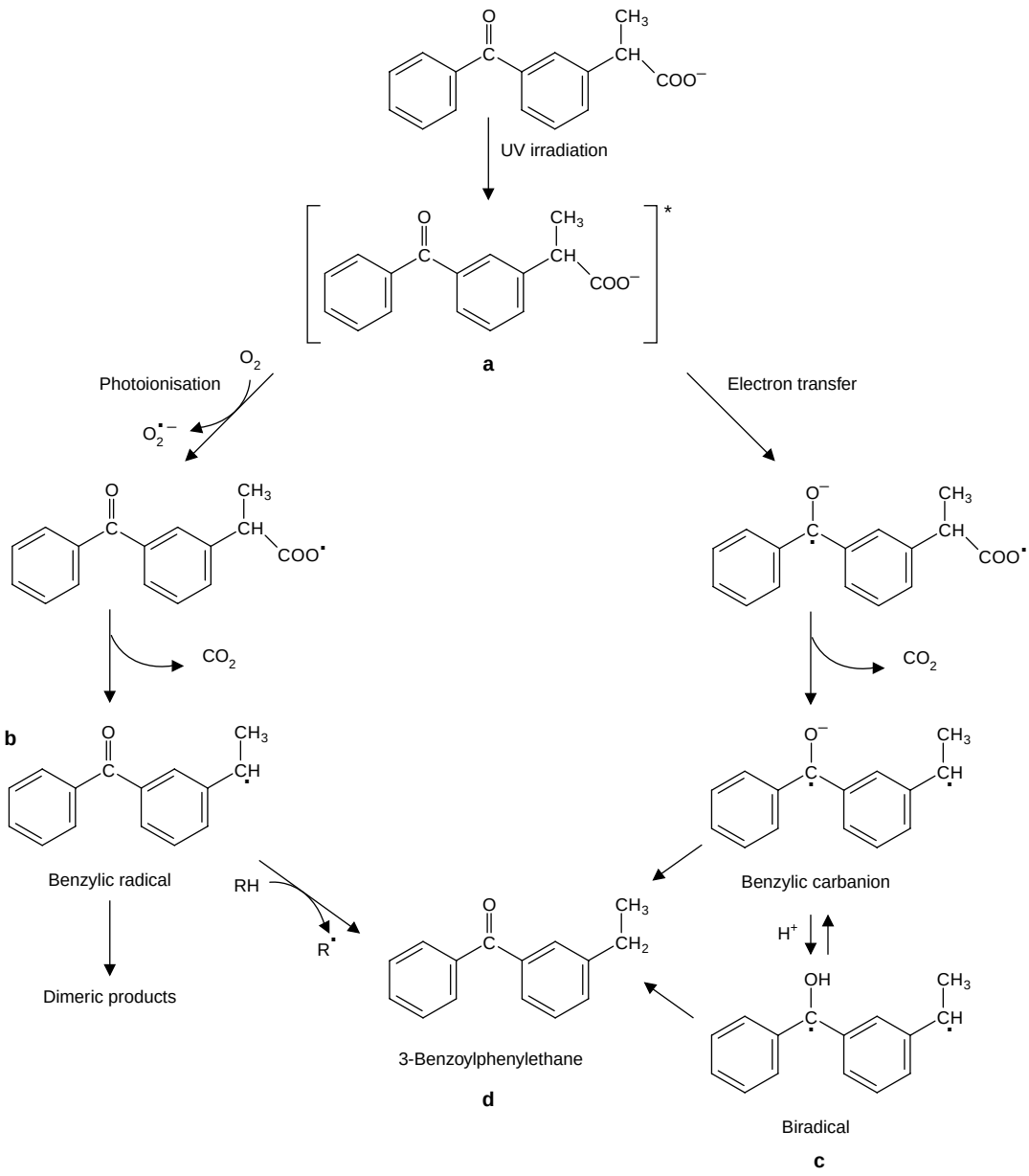

Fig. 4. Mechanism of the photodecarboxylation of ketoprofen. (**a**) Ketoprofen excited state; (**b**) ketoprofen benzylic radical; (**c**) ketoprofen biradical; and (**d**) 3-benzoyalphenylethane. **UV** = ultraviolet; **[ ]*** = excited state.

In addition, the role of excipient should not be totally excluded in the development of contact dermatitis: 11of 33 tested patients were positive to lavender or neroli oil.[12] Utilising photopatch testing, Pigatto et al.[27] also demonstrated frequent positive cross-reactions of ketoprofen with cinnamic aldehyde and balsam of Peru used as fragrance mix.

From October 1995 to December 1997, 42 cases of photocontact dermatitis attributable to ketoprofen have been collected by the Swedish Adverse Drug Reactions Advisory Committee.[41] The average treatment time was 28 days (median 21) and ranged from 1 to 50 days.

An analysis of adverse drug reactions of all locally administered drugs (including cutaneous or percutaneous, pulmonary, ocular, buccal, nasal, intra-articular and auricular administration) in the database of the Center of Pharmacovigilance of the Midi-Pyrénées region of France over a 5 year period revealed that topical NSAIDs were the most frequently reported agents (20% of a total of 128 cases) and that these reactions occurred more often in younger individuals. Indeed, 43% of them were between 30 and 45 years of age.[42]

4. Discussion

Although all NSAIDs could potentially induce phototoxic reactions, the higher frequency of such adverse reactions with ketoprofen could be accounted for by its chemical structure (carbonyl function) and the variety of chemical reactions that give rise to phototoxic effects.[18] Furthermore, in contrast to some drugs such as fenofibrate which promotes only photoallergic reactions, ketoprofen induces both phototoxic and photoallergic reactions.[21]

It should be emphasised that some chemical structures such as the benzophenone moiety have been involved in photoallergic contact dermatitis, although unidentified individual factors contribute to these immune-mediated reactions.[43] The diphenylketone group of ketoprofen plays a key role in photocontact sensitivity.[28,44] The cross-reactivities for photoallergic reactions of ketoprofen with other drugs such as fenofibrate or tiaprofenic acid could be explained by the presence of a ketonic group.[27,28,43]

The main therapeutic claim for topical NSAIDs is that they exert their effect through local penetra-

Table I. Ketoprofen-induced photocontact dermatitis case reports after application of topical ketoprofen gel 2.5% with photopatch test or cross-sensitivity reaction investigations

Study	Number of patients	No. of patients with a positive photopatch test	No. of patients with positive cross sensitivity
Alomar et al.[29]	3	3	
Cusano et al.[30,31]	8	7	
	1	1	Ibuproxam (1/1)
Romaguera et al.[32]	37	20	
Mozzanica et al.[33]	10	8	Ibuproxam + flurbiprofen (1) Tiaprofenic acid (2)
Lanzarini et al.[34]	1	1	
Tosti et al.[35]	7	1	
Catrani et al.[36]	5	5	
	5	5	
Jeanmougin et al.[26]	2	2	Fenofibrate (2/2)
Bastien et al.[37]	5	5	
Le Coz et al.[38]	12	12	Tiaprofenic acid (12/12) Fenofibrate (8/12) Benzophenone (11/12)
Adamski et al.[39]	11	10	Fenofibrate (5/9) Phenylbutazione (3/10) Oxubutazone (1/10)

tion and thus avoid the systemic adverse effects (particularly gastric), of oral NSAIDs. However, the evidence suggests that topical forms diffuse directly into soft tissue, penetrating the synovial joint mainly via the systemic circulation.[45,46] However, the evidence that such applications result in clinically significant synovial fluid concentrations is scant.[47] Recently, Moore et al. undertook a quantitative systematic review of 86 randomised controlled trials designed to examine the effectiveness and tolerability of topical NSAIDs.[6] The results suggested that in acute pain conditions, ketoprofen, felbinac, ibuprofen and piroxicam had significant efficacy, although benzydamine and indomethacin were no different from placebo. Nevertheless, we lack comparisons with other treatments, such as oral NSAIDs, topical rubefacients or paracetamol (acetaminophen) to define a therapeutic role for topical NSAIDs. Of the 86 trials reviewed, only 5 compared topical with oral NSAIDs. Furthermore, many trials included small series of patients and short durations of treatment.

Finally, combining the results from different studies of patients with different musculoskeletal conditions may introduce errors, and a reliable meta-analysis of these agents is not straightforward.[48] In a review of the literature on the benefit of topical NSAIDs for musculoskeletal diseases, Vaile et al.[5] concluded that although several studies claim a benefit for topical NSAIDs compared with placebo, the trials against intra-articular corticosteroids and rubefacients are either lacking or less conclusive. A clear indication of topical NSAIDs has yet to be defined for arthropathies. The bulletin from the UK Medicines Resource Centre is highly critical of the benefit/risk and cost/benefit of topical NSAIDs, and notes that £30 million is spent each year in the UK on prescribing topical NSAIDs.[45]

5. Conclusion

The higher frequency of photosensitivity reactions with ketoprofen could be accounted for by its chemical structure and the variety of chemical reactions that give rise to phototoxic effects.

In many European countries, topical NSAIDs are sold as over the counter drugs. Patients may obtain them without any medical supervision and may exceed recommended durations of treatment. Their use may also be increased by the practice of certain sports.

The widespread and repeated use of these agents may lead to sensitisation, incurring a greater risk of systemic allergic reactions with oral NSAIDs or other drugs recognised to induce cross-reactions. Physicians and pharmacists should advise patients and inform them of the risk of topical NSAIDs dispensed as over-the-counter drugs.

Acknowledgements

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