

Drug-induced Photosensitivity

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ABSTRACT Ultraviolet radiation is considered the main environmental physical hazard to the skin. It is responsible for photoaging, sunburns, carcinogenesis, and photodermatoses, including drug-induced photosensitivity. Drug-induced photosensitivity is an abnormal skin reaction either to sunlight or to artificial light. Drugs may be a cause of photoallergic, phototoxic, and photoaggravated dermatitis. There are numerous medications that can be implicated in these types of reactions. Recently, non-steroidal anti-inflammatory drugs have been shown to be a common cause of photosensitivity. As both systemic and topical medications may promote photosensitive reactions, it is important to take into consideration the potential risk of occurrence such reactions, especially in people chronically exposed to ultraviolet radiation.

KEY WORDS: photoallergic contact dermatitis, photosensitizing agents, phototoxic dermatitis

INTRODUCTION

Drug-induced photosensitivity is an undesirable effect of topically applied or systemically administered pharmaceuticals, followed by exposition to sunlight, mainly ultraviolet A (UVA) or/and ultraviolet B (UVB) radiation as well as visible light. Such reactions usually affect the skin but the eye involvement is also possible. There has recently been a substantial increase of drug-induced photoreactions as a consequence of the ozone-layer depletion that allows intense sunlight to reach the surface of Earth.

Photosensitivity may be triggered by UVA and UVB radiation in individuals who take certain medications or who suffer from particular disorders. Photosensitivity skin lesions represent 8% of all cutaneous adverse drug reactions (1-3).

Photosensitivity might be associated with different mechanisms such as phototoxicity, photoallergy, pellagra, pseudoporphyria, lichenoid, and lupus erythematosus reactions. The most common are phototoxicity and photoallergy. The difference between them is shown in Table 1 (4-5). There are numerous drugs which can trigger sun-related skin reactions. Table 2 illustrates which drugs may induce photoallergic or phototoxic reactions (6).

PHOTOTOXICITY

Phototoxicity is an abnormal chemical reaction induced by light. Phototoxic drugs are those which are able to absorb radiation. They must have a single or double bond or halogenated aromatic rings in the

Table 1. Phototoxic versus photoallergic reaction (4)

| | Phototoxicity | Photoallergy |
|----------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Onset of reaction | minutes to hours | 1-3 days |
| Incidence | more common | less common |
| Required exposure to agent | single | more than one |
| Mechanism | reactive oxygen radicals cause change in skin molecules leading to long-term damage or cell death | UV rays activate immune system promoting activation of macrophages which leads to the formation of typical for contact dermatitis skin lesions |
| Immunologically mediated | no | yes, type IV and its subtypes (5) |
| Localization of lesions | confined to the sun-exposed skin area | outbreak is not limited to the sun-exposed skin, it can spread to the whole body area (less inclined to affect submental, retroauricular areas and upper eyelids) |
| Duration of the reaction | active process (sometimes for years) even after the triggering factor was removed | until the trigger is removed, it can persist very rarely for years without further exposure to the photosensitizing agent |
| Clinical manifestation | exaggerated sunburn with blistering, desquamation and hyperpigmentation | dermatitis |
| Concentration relation | concentration related | concentration not related |

*UV: ultraviolet

molecule that determine the absorption spectrum. Typically wavelength causing photosensitive reactions is above 310 nm.

A molecule that absorbs photons is called a chromophore. The energy of the photon causes promotion of the electrons from a ground state to an excited state. The so-called singlet or triplet state of the photosensitizer is an unstable state and exists only for a short time, typically up to 10^{-10} s for singlet and 10^{-6} s for triplet states. Returning to a ground state is associated with a discharge of energy by radiation, heat emission, or a chemical reaction that results in the formation of a photoproduct. The energy transfer from excited photosensitizer to oxygen leads to the production of excited single oxygen atoms that can participate in lipid and/or protein oxidation or deoxyribonucleic acid (DNA) damage. That leads to direct cellular damage and may induce an immunological inflammation (7). DNA damage may also lead to photogenotoxicity that results in cancerogenesis and development of squamous cell carcinoma.

PHOTOALLERGY

Photoallergy may be elicited by systemic as well as topical drugs. In both cases, photoallergic dermatitis is a delayed, T-cell mediated hypersensitivity reaction (IV type Coombs and Gell classification). Photoallergic responses produced by systemically administered substances are much rarer than those caused by topically applied drugs. Previous sensitization to the pho-

toallergen is required. Two mechanisms of photoallergic reactions have been proposed. In the first case, a stable photoproduct formed from the reaction of the drug with UV radiation serves as a hapten. A complete antigen is created by a combination of a hapten and a carrier molecule. Alternatively, a drug able to absorb light might be shifted to an excited, unstable state. A molecule reverting to its ground state results in energy release that may lead to conjugation with a carrier. After formation of the complete antigen, the mechanism of photoallergic dermatitis is identical to the pathogenesis of allergic contact dermatitis. The antigen is processed and presented by Langerhans cells, in association with human leukocyte antigen (HLA) II antigens. T lymphocytes are activated by Langerhans cells in regional lymph nodes. Skin lesions will occur when activated T-cells recirculate to the light-exposed sites and recognize the photoallergen (8).

CLINICAL FEATURES

Phototoxic reactions may occur in patients of any age, predominantly in women. Symptoms of phototoxic skin reaction resemble an exaggerated sunburn and are limited to the sun-exposed areas.

Phototoxicity provokes the occurrence of erythema and edema within minutes to hours. Vesiculation and blistering are rare. Persistent hyperpigmentation is also possible. The reaction is an active process of skin cell damage and can persist for years, long after the triggering factor has been removed (4).

Table 2. Common phototoxic and photoallergic drugs (6)

| Group of drugs | Medication | Phototoxic reaction | Photoallergic reaction | Action spectrum |
|------------------------------------|-----------------------|---------------------|------------------------|----------------------|
| Oral treatment | | | | |
| Cardiovascular and diuretic agents | Furosemide | + | - | Unknown |
| | Amiodarone | + | - | UVA |
| | Quinidine | + | + | UVA |
| | Thiazides | + | + | UVA/UVB |
| Antibiotic | Dapsone | - | + | Unknown |
| | Sulfonamide | + | + | UVB |
| | Tetracycline | + | - | UVA/UVB |
| | Ciprofloxacin | + | - | UVA |
| Antifungal | Griseofulvin | + | - | UVA |
| | Ketoconazole | + | - | Unknown |
| DMARD | Hydroxychloroquine | - | + | Unknown |
| NSAID | Naproxen | + | - | UVA |
| | Piroxicam | | + | UVA |
| | Tiaprofen | + | + | UVA |
| | Ibuprofen | + | - | UVA |
| | Ketoprofen | + | + | UVA |
| Topical treatment | | | | |
| Antineoplastics | 5-FU | + | + | Unknown |
| Furocoumarins | Psoralen | + | + | UVA |
| Keratoplastics | Coal tar | + | - | UVA |
| PDT Pro-photosensitizer | 5-Aminolevulinic acid | + | - | UVA/visible spectrum |
| NSAID | Ketoprofen | + | + | UVA |
| | Naproxen | + | + | UVA |

*UVA: ultraviolet A; UVB: ultraviolet B; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal anti-inflammatory drugs; 5FU: Fluorouracil; PDT: photodynamic therapy

Photoallergic dermatitis occurs in patients of any age. Men are affected more commonly than women. Onset of these reactions is 24-72 h after exposure. Photoallergic dermatitis generally affects the light-exposed areas: the face, neck, upper chest, and dorsum of hands. Lesions may spread to unexposed areas. Symptoms of photoallergic dermatitis are similar to those of contact dermatitis. Consequently, desquamation and residual hyperpigmentation occur and can persist for more than a year. The predominant form of this reaction is eczematous (4).

DRUGS ASSOCIATED WITH PHOTOSENSITIVITY

This paper describes drug-induced photosensitivity related to: non-steroidal anti-inflammatory drugs (NSAIDs), cardiovascular drugs, tetracyclines, quinolones, voriconazole, and vemurafenib. NSAIDs are the most common cause of drug-induced photosensitivity. Cardiovascular drugs are one of the medications

most widely used by elderly patients. Tetracyclines and quinolones are often prescribed by dermatologists and physicians of other specialties due to their antimicrobial properties. Voriconazole and vemurafenib may lead to severe photosensitivity reactions, but their photosensitive potential is not well-known.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs are widely prescribed by physicians of all specialties. They have been found to elicit a high level of adverse photosensitivity. Some NSAIDs, including ibuprofen and naproxen, are also available over-the-counter (9). Both systemic and topical administration of non-steroidal anti-inflammatory drugs may promote photoallergic and phototoxic reactions.

NSAIDs are a heterogeneous group. Photosensitivity reactions induced by the use of ketoprofen, naproxen, tiaprofenic acid, ibuprofen, diclofenac, piroxicam, celecoxib, benzydamine, and etofenamate have been reported (10-15).

Ketoprofen

Ketoprofen has been shown to cause most cases of NSAIDs-induced photosensitivity (9-10). Its administration may induce phototoxic, photoallergic, and phototaggravated contact dermatitis.

Ketoprofen-induced phototoxicity is dependent on the presence of this drug in the skin and may occur in anyone, given sufficient UV radiation. According to Nakajima *et al.* (16), ketoprofen phototoxicity may involve production of oxygen free radicals, which are highly reactive towards proteins and lipids. In addition, Constanzo *et al.* (17) demonstrated that ketoprofen irritation causes the photolysis of erythrocyte suspension. Photolysis of erythrocytes has been noted as an indicator of membrane damage. The use of radical scavengers resulted in significant reduction of photosensitized lysis of red blood cells, suggesting the involvement of free radicals in these processes.

According to Chouini-Lalanne *et al.*, (18) DNA may be another biological target of ketoprofen-induced phototoxicity. Ketoprofen may cause DNA cleavage *in vitro* upon irradiation. In the presence of ketoprofen, pyrimidine dimers are formed by an energy transfer mechanism involving single strand breaks.

Photallergy due to ketoprofen is a classical delayed T-cell mediated hypersensitivity reaction. Ketoprofen is a propionic acid derivative, as well as a substituted benzophenone. Considering the chemical structure of ketoprofen, many authors (19-20), point out benzophenone moiety as a cause of photoallergic dermatitis induced by this drug. Benzophenone moiety may also explain cross-reactions between ketoprofen and benzophenone-derived chemicals, i.e. benzophenone-3 (component of sunscreen creams), tiaprofenic acid and fenofibrate.

Cross-reactivity between ketoprofen and nonbenzophenone-containing molecules has recently been also observed. Photopatch testing was positive for fenitichlor, tetrachlorosalicylanilide, triclosan, and hexachlorophene in patients with contact photodermatitis to ketoprofen (21). All these molecules, including ketoprofen, share a benzene ring linked to an oxygen group, which may be involved in a cross-photosensitization phenomenon. However, a benzene ring linked to an oxygen group is not specific for ketoprofen.

Patients with photoallergy due to ketoprofen often present with photosensitivity to octocrylene. In the study by Karlsson *et al.* (22), all patients who had positive photopatch tests to ketoprofen also had positive photopatch tests to octocrylene. Patients who experienced photoallergic reaction to ketoprofen should avoid sunscreens containing benzophenone-3 and octocrylene (23).

There are numerous case reports of photosensitivity reactions in the literature, mainly to topical ketoprofen.

Matthieu *et al.* (24) performed patch tests and photopatch tests in 20 patients suspected of ketoprofen-induced dermatitis. Photoallergic contact dermatitis to ketoprofen was confirmed in 17 patients. Patch and photopatch tests demonstrated a contact allergy in 1 patient and a photoaggravated contact allergy in 2 patients. Severe skin lesions requiring systemic corticotherapy were present in 47% of patients. 26% of patients required hospitalization. Prolonged photosensitivity was observed in one patient.

Caterina *et al.* (25) reported 2 cases of photodermatitis due to systemic ketoprofen in patients with previous reactions to topical application of this drug. Both patients developed eczematous skin lesions within photoexposed areas of a body after oral administration of ketoprofen. These cases highlight a possibility of photosensitivity reactions due to oral ketoprofen in patients with a history of photocontact dermatitis after previous topical application of this medicine.

There were 3 cases of photoallergic contact dermatitis after topical use of ketoprofen reported in patients diagnosed at the Department of Dermatology of the Poznan University of Medical Sciences. All patients experienced eczematous skin lesions. In 2 patients skin lesions had a bullous manifestation. In all cases, the skin lesions were restricted to the skin area of drug application. The delay between the application of ketoprofen and the reaction was between 2 and 60 days. One patient presented with a recurrence of the photosensitivity phenomenon after 1 year since the previous reaction (26).

Piroxicam

Piroxicam has been known as an important photosensitizer since 1983, when Fjellner (27) reported the first case of piroxicam-induced photosensitivity. Fjellner observed an erythematous-bullous eruption on light-exposed skin areas in a woman who was treated with systemic piroxicam due to rheumatoid arthritis. Photopatch tests were performed and showed a positive reaction to piroxicam. There are numerous case reports in the literature of photodermatitis caused by both oral and systemic piroxicam (9,28).

Photosensitivity induced by piroxicam may result in both phototoxic and photoallergic reactions and can be due to topical or systemic administration (29). Piroxicam is widely used in treatment of rheumatologic diseases, and 1-3% of patients taking this drug experience adverse cutaneous reactions (28). Upon

low UVA irradiation, a photoproduct of piroxicam is formed which is chemically similar to thiosalicylic acid (moiety of thimerosal). This mechanism may be responsible for cross-reactivity between piroxicam, thiosalicylic acid, and thimerosal (30). Most data do not support cross-reactivity between different oxycams (10,31), although a case photodermatitis elicited by piroxicam with a positive photopatch test to other oxycams has been reported (29).

Benzydamine

Benzydamine is an indazole non-steroidal anti-inflammatory drug. It is available in Poland as a vaginal solution, mouth aerosol, and throat lozenges. Photosensitivity from benzydamine may be underdiagnosed and has been occasionally described.

Benzydamine has phototoxic and photoallergic properties (32). Used as a mouth aerosol or solution, it can induce cheilitis and chin dermatitis as a manifestation of photoallergy.

Canelas *et al.* (33) investigated photocontact allergy to benzydamine in a group of 74 patients. They performed photopatch tests with an extended series of allergens including benzydamine. In 10 patients a positive photopatch test to benzydamine was detected. Nine patients presented with lower lip cheilitis and one lichenified eczema on photoexposed areas (face, neck, upper chest, forearms, dorsum of hands).

Another description of photocontact allergy caused by benzydamine was published by Elgezua *et al.* (34). They reported a case of a photoallergic hand eczema due to benzydamine present in a gynecological washing solution. Eczema presented on the dorsum of both hands. The rest of the skin, including external genital organs, was unaffected. The diagnosis was confirmed using photopatch tests.

Diclofenac

Although diclofenac is a well-known possible photosensitizer, there are only a few reports of it causing photosensitivity reactions.

Portuguese researchers performed photopatch tests in 30 patients with suspected photoaggravated facial dermatitis or systemic photosensitivity. One patient had a positive reaction to diclofenac. Diclofenac-induced photoallergy was attributed to systemic photosensitivity (31).

Kowalick *et al.* (35) reported a case of photoallergic contact dermatitis from topical diclofenac in a 77-year old female patient who was treated with 3% topical diclofenac due to actinic keratosis. The patient developed exsudative, itching erythema on the right

cheek where the topical diclofenac was applied. She presented with positive patch and photopatch test results.

One case of photoallergic contact dermatitis due to topical use of diclofenac was reported in a 29-year-old male patient who was diagnosed at the Department of Dermatology of the Poznan University of Medical Sciences. The patient presented with eczematous skin lesions on the right foot 7 days after application of the drug (26).

Cardiovascular and diuretic agents

Amiodarone

Amiodarone is a systemic antidysrhythmic drug that may provoke a wide range of photosensitive reactions. The phenomenon is UVA and visible light dependent and may be provoked by glass-transmitted light even on cloudy days or during winter time. During sun exposure an immediate erythema, stinging, or burning may occur. The agent is prone to inducing exaggerated sunburn, pseudoporphyria, hyperpigmentation, and delayed erythema. Urticaria and edema may occur with higher doses. A minority of patients may present an abnormal golden-brown or unsightly grey pigmentation that does not disappear immediately after drug cessation and may persist for months along with photosensitivity. When amiodarone is a drug of last resort, dosage reduction combined with photoprotection is the only possibility of management (3).

Statins

Statins are one of the most frequently administered lipid-lowering agents worldwide (36). Cutaneous reactions have been reported among the multiple adverse effects of these 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, mainly due to photosensitivity. Photophysical and photochemical results indicate that singlet oxygen formation generated by the phenanthrene-like photoproduct of atorvastatin can induce phototoxic reaction (36). UVB-mediated phototoxicity due to atorvastatin was reported (37). Rosuvastatin was described as a potential sensitizer through its dihydrophenanthrene-like compound (38).

Fluvastatin has been proven to act as a phototoxic agent after UVA irradiation through its benzocarbazole-like photoproduct. It has been reported that the phototoxic compound of fluvastatin mainly caused necrosis of the analyzed keratinocytes (39).

Simvastatin and pravastatin are known causes of photoinduced erythema multiforme (40).



The literature of case reports of phototoxic and photoallergic skin reactions of HMG-CoA reductase inhibitors is scarce. Thus it may appear that photosensitivity is not a common clinical problem in this group of drugs.

Thiazides and Furosemide

Thiazide diuretics may provoke exaggerated sunburn, which if recurrent, may induce chronic actinic dermatitis. Some patients present lupus and lichen planus-like eruptions. The photochemical activity is due to a chlorine substituent which is present in the structure of thiazides and furosemide. The UV dissociation of the chlorine substituent leads to reactions with lipids, proteins, and DNA (7). Photosensitivity is idiosyncratic and rare. The management involves a substitution of the thiazide with a relatively less photoactive loop diuretic (2).

Quinidine

The photosensitive reaction provoked by quinidine sulphate has been known since 1942. The mechanism is a type-IV allergic reaction (2).

Antibacterial drugs

Tetracyclines

Tetracyclines are one of the most frequent photosensitizing agents among antibacterial drugs. There is a significant difference in the phototoxic index among the derivatives.

Demethylchlortetracycline and doxycycline have the highest phototoxic potential; tetracycline and oxytetracycline are less photoactive. Minocycline and lymecycline have the lowest index of phototoxicity among tetracyclines (41-43). Layton *et al.* (44) reported that the phototoxic phenomenon of doxycycline is dose dependent (Table 3).

The typical clinical manifestation of phototoxic reaction to tetracycline is sunburn, which may be associated with papular eruption or blistering (43). Tetracycline-induced photoonycholysis may also occur, usually at least 2 weeks after drug administration (45).

Table 3. Dose-dependent phototoxicity to doxycycline (44)

| Dose of doxycycline (mg/day) | Incidence of phototoxicity (%) |
|------------------------------|--------------------------------|
| 100 | 3 |
| 150 | 20 |
| 200 | 42 |

Yap *et al.* (46) reported a case of solar urticaria caused by tetracycline. A 28-year-old woman treated with oral tetracycline developed macular erythema and pruritus. Skin lesions were restricted to the sun-exposed area of the body. Photopatch testing demonstrated urticarial reaction within 15 minutes. After cessation of tetracycline, phototesting was negative.

Quinolones

Quinolones are broad spectrum antibacterial drugs which may induce photosensitization reactions of a varying degree of severity. There are four generations of quinolones. Presently, the therapeutic use of first generation quinolones is very limited in Europe, although some of them are still marketed in several countries, for instance nalidixic acid and piperimidic acid (47). There are many reports proving the phototoxicity potential of representatives of all quinolone generations, for example nalidixic acid, piperimidic acid, ciprofloxacin, fleroxacin, norfloxacin, moxifloxacin, lomefloxacin, ofloxacin, and rufloxacin (48).

Quinolones mostly cause phototoxic reactions, although there are also some reports of photoallergy. There has been evidence of the photoallergic potential of lomefloxacin and nalidixic acid (49,50).

The study of Wagai *et al.* and Marutani *et al.* demonstrate that lomefloxacin is the most phototoxic of fluoroquinolones. In the first study its photosensitizing action was stronger than nalidixic acid. Furthermore, empirical studies have suggested that moxifloxacin may be a mild photosensitizer. Methoxy group substitution may reduce the photosensitizing activity of moxifloxacin (48,51,52).

Novel drugs

Several recently produced drugs have photosensitising potential. Such drugs include antifungal voriconazole (53,54) or anticancer drugs eg. vemurafenib. Voriconazole, which is a triazol antifungal agent and is widely used as a prophylaxis in patients after transplantations, exhibits its phototoxic potential in particular during long-term treatment. This agent may be associated with chronic phototoxicity, accelerated

Table 4. Classification criteria for photopatch test reaction (54)

| Point Scale | Skin lesion type |
|-------------|----------------------------------|
| 0 | No reaction |
| 1 | Erythema |
| 2 | Erythema and dermal infiltrate |
| 3 | Erythema and papulovesicles |
| 4 | Erythema and blisters or erosion |

Table 5. Interpretation of photopatch test results (54)

| Non-irradiated site | Irradiated site | Conclusion |
|---------------------|-----------------|---------------------------|
| - | - | No reaction |
| - | + | Photoallergic reaction |
| + | + | Contact reaction |
| + | +++ | Phototaggravated reaction |

photo-aging, and, most likely, development of squamous cell carcinoma. Vemurafenib is an orally administered inhibitor of BRAF kinase used in the treatment of late-stage melanoma (55,56). During the treatment, patients frequently experience immediate phototoxic reactions among other cutaneous side effects. Studies have shown that this reaction is UVA dependent and probably related to decreased vitamin PP level and increased porphyrins levels (57). It is essential when developing new drugs to predict the potential for phototoxicity of its compounds. Over the past few years some effective methodologies have led to the formation of some regulatory guidelines of drug photosafety (58).

Over-the-counter photosensitisers

Cosmetics such as sunscreens or anti-aging products that contain benzophenones or octocrylenes may also be a cause of photosensitive reactions (58,59).

Some photosensitizers such as ibuprofen, naproxen, diclofenac, and some plant extracts eg. *Hypericum perforatum* are available over-the-counter in Poland.

Patients are seldom aware of the potential risk of an adverse skin reaction and use medications without consulting their physician. Thus, it is important to educate and increase awareness of possible photosensitivity.

Photopatch testing

Phototesting is a helpful tool in diagnosing drug-induced photosensitivity. Ketoprofen, etofenamate, piroxicam, and benzydamine are the only NSAIDs included in the standard photopatch test series (60). This procedure should not be performed while dermatitis is active. Photopatch testing should be undertaken on skin that has not been affected for the last 2 weeks to avoid the effects of the so-called the "angry back" syndrome. The best choice for the testing area is the skin of the upper back, avoiding the paravertebral area (61). Patch series have to be applied in a

duplicate set on either side of the vertebrae. One set is fixed to the skin for 24 hours. After 24 hours it is removed and irradiated with UVA (psoralen combined with ultraviolet A (PUVA) fluorescent lamp of broad spectrum) of 5 J cm². The control non-irradiated set can be fixed for either 24 or 48 hours, after which is removed. The irradiated test site is read before, immediately, and 48, 72, and 96 hours after irradiation. The un-irradiated test site has to be evaluated after patch test removal as well as after 48, 72, and 96 hours. Erythema, dermal infiltrate, papulovesicles, blisters, and erosion indicate a positive reaction (Table 4) (62). A positive response at an irradiated site and negative at a control site is interpreted as a positive photopatch test reaction. Positive reaction at both sites is regarded as a contact reaction that may be aggravated by the UV light (Table 5) (61,62).

CONCLUSION

Drug-induced photosensitivity may cause serious diagnostic difficulties, especially when it comes to systemic medications. Knowledge of drugs prone to inducing such an adverse reaction is crucial when choosing the right treatment modality. It is important to establish the potential risk of causing a photosensitive reaction before beginning phototherapy or laser therapy, especially in patients chronically exposed to sunlight due to professional reasons.

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