

COMMONLY USED PHOTSENSITIZING MEDICATIONS: THEIR ADVERSE EFFECTS AND PRECAUTIONS TO BE CONSIDERED

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ABSTRACT

Drug-induced photosensitivity of the skin is drawing increasing attention. In past few decades, photosensitivity has been reported with array of drugs, and is now recognized as a noteworthy clinical problem by clinicians, regulatory authorities and the pharmaceutical industry. The photosensitivity is of two types *i.e.*, phototoxicity and photoallergy. Phototoxic disorders have a high incidence, whereas photoallergic reactions are much less frequent in human population. In phototoxic reactions, there is direct damage to the tissue whereas photoallergic reactions are immunologically mediated. Hundreds of substances, chemicals, or drugs may invoke phototoxic and photoallergic reactions. Photosensitivity reactions are recognized as unwanted adverse effects of an array of commonly administered topical or systemic medications, including nonsteroidal anti-inflammatory agents, antifungal, and antimicrobials. In order to avert photosensitive reactions, it is vital to ascertain the photosensitizing properties of such substances before drugs are introduced in therapy or products made available in the market. In the present review, we have attempted to cover various essential aspects of photosensitizing medications including differences between phototoxic and photoallergic reactions, the most common photosensitizers and clinical features and diagnosis of phototoxicity and photoallergy.

Keywords: phototoxic reaction, photoallergic reaction, photosensitivity, photosensitizers.

INTRODUCTION

Photosensitivity (sun sensitivity) is inflammation of the skin induced by the combination of sunlight and certain medications or substances. This causes redness of the skin similar to sunburn. Photosensitive skin reactions occur when human skin reacts to ultraviolet radiation or visible light abnormally. When a drug induces photosensitivity, exogenous molecules in the skin absorb normally harmless doses of visible and UV light, leading to an acute inflammatory response. It has been recommended that all new drugs should be screened for photosensitizing effects before they are subjected to clinical trials, in order to reduce potential distress to patients.^{1,2}

Photosensitivity caused by drug reactions may be defined as unwanted pharmacological effects produced when the skin is sensitized by topical or systemic medications, or both, and exposed to UV rays, either artificially or naturally. Such peculiar and often distressing photobiologic reactions are commonly considered to be the undesirable adverse effects of commonly administered drugs such as phenothiazines, amiodarones (antiarrhythmics), nonsteroidal anti-inflammatory agents, and antimicrobials. Photosensitivity has frequently been associated with local antiseptics, antifungals (griseofulvin), and the antimicrobials *i.e.*, nalidixic acid, fluoroquinolones, sulfonamides, tetracyclines, and antiprotozoans. Although such reactions rarely involve the morbidity and mortality seen with other adverse effects, including toxic epidermal necrolysis, Stevens-Johnson syndrome, anaphylaxis, or systemic toxicity, they do constitute a common dermatologic and pharmaceutical concern.³⁻⁸

Photosensitivity reactions

Photosensitivity is an adverse cutaneous reaction that results when a certain chemical or drug is applied topically or taken systemically at the same time when a person is exposed to UVR or visible light. Photosensitivity reactions may be more specifically categorized as phototoxic or photoallergic in nature. Phototoxicity is much more common than photoallergy. Photosensitivity reactions are hardly predictable. They can occur in persons of any age but are more common in adults than children, possibly because adults are usually exposed to more medications and topical agents. The degree of photosensitivity varies among individuals *i.e.*, with similar intensity not everyone will have a photoreaction. A person who has a photoreaction after a single exposure to an agent may not react to the same agent after repeated exposures; on the other hand, person who is allergic to one chemical may develop photosensitivity to related chemical. Several factors, such as quantity and location of the chemical or drug on/in the skin; quantity, spectrum, and penetration of the activating radiation; thickness of the horny layer; degree of melanin pigmentation; immunological status of the affected person, may influence the features of photosensitivity reactions. Person's immunological status is very important because photosensitivity reactions are found frequently in immunocompromised human immunodeficiency virus (HIV)-infected patients.^{8, 9} If patient exhibits photodistributed skin problems of unknown origin, the possibility of HIV infection should be suspected. Generally, these reactions can be divided into two mechanisms, 1) phototoxic reactions and 2) photoallergic reactions. Phototoxic drugs are much more common than photoallergic drugs.



Phototoxic reactions

In phototoxic reactions, the drug may become activated by exposure to sunlight and cause damage to the skin. The skin's appearance resembles sunburn, and the process is generally acute (has a fast onset). Ultraviolet A (UVA) radiation is most commonly associated with phototoxicity, but ultraviolet B (UVB) and visible light may also contribute to this reaction. A phototoxic reaction typically clears up once the drug is discontinued and has been cleared from the body, even after re-exposure to light.

Phototoxicity is a form of photosensitivity that is not depended on an immunologic response. Phototoxic reactions are dose dependent and will occur in almost any one who takes or applies an adequate amount of the offending agent and UVR, but the dose necessary to induce such a reaction varies among individuals. Phototoxic reactions can appear on first exposure to the agent and demonstrate no cross-sensitivity to chemically related agents.^{1,8}

Photoallergic reactions

In photoallergic reactions, the ultraviolet exposure changes the structure of the drug so that is seen by the body's immune system as an invader (antigen). The immune system initiates an allergic response and cause inflammation of the skin in the sun-exposed areas. These usually resemble eczema and are generally chronic (long-lasting). Many drugs in this family are topical drugs. This type of photosensitivity may recur after sun exposure even after the drug has cleared from the system. Photoallergy is a form of photosensitivity that is immunologically mediated. Photoallergic reactions develop only in sensitized persons and are not dose dependent, although a sensitized person is likely to get a stronger reaction at a much higher dose.²

PHOTOTOXICITY

Phototoxic reactions result from direct cellular damage produced by the photoproducts, provided enough of the chemical and radiation are present. No immunologic mechanisms are involved in phototoxic reactions, so they can manifest themselves during an initial exposure. Phytophotodermatitis caused by bergamot oil, parsley, celery, dates, and other plants containing the furocoumarins is a classic example of phototoxic reaction. At a molecular level, most phototoxic reactions (*i.e.*, in the case of acriflavine, porphyrins, chlorothiazide, tetracyclines, nonsteroidal anti-inflammatory agents, quinolones, and certain dyes, such as methylene blue) develop in the presence of oxygen, in which free radicals resulting from photo-oxidation and peroxidation processes cause injury to cell nuclei, cytoplasm, and cellular membrane components.^{4,11,12}

Phototoxicity reactions to psoralens, although rarely requiring molecular oxygen, are for the most part oxygen independent. In those cases, UV-A–induced covalent binding (formation of cyclobutane dimers) between the

chemical and the molecules of DNA occurs. Similar dimers are formed between chlorpromazine and RNA molecules. The factors that strongly influence the incidence, intensity, and clinical features of phototoxic reactions include the nature, concentration, absorption, and pharmacokinetics of the drug; quantity and spectrum of radiant energy; and factors related to the skin thickness of the stratum corneum, quantity of melanin, temperature, and humidity. Most phototoxic eruptions are characterized by rapid onset of a burning sensation, erythema, edema, and sometimes vesiculation. Eruptions develop shortly after exposure to light with intensity increasing in a dose-dependent manner. Persons with light skin seem to be more prone to develop phototoxic reactions, whereas in darker skins melanin offers some degree of protection. Pseudoporphyria, a condition clinically similar to porphyria cutanea tarda but lacking abnormalities in porphyrin metabolism, has been described as a variant of a phototoxic reaction in conjunction with sulfonamides, griseofulvin, nalidixic acid, and the tetracyclines.^{3,8,13,14}

PHOTOALLERGY

Photoallergy refers to immunologically mediated photosensitivity reactions, in which immediate (humoral-mediated) hypersensitivity, delayed (cell-mediated) hypersensitivity, or both develop to a photoactivated compound (a drug or chemical) transformed into a hapten or a complete antigen during radiation.^{15,16} In contrast to phototoxic reactions, photoallergy is usually elicited by the longer UV-A wavelengths. Photoallergic drug responses develop only in sensitized persons and are not dose dependent. Cell mediated responses require a latency period for the immunologic memory to develop after the first contact with the photosensitizer; on subsequent exposures the elicitation of response is shorter. The delayed type of photoallergy is more frequent. According to the mode of administration of the photosensitizer, photoallergic reactions can be classified as either contact photoallergic dermatitis or photoallergy induced by systemic agents. Several factors may influence the incidence, intensity, and some clinical features of photoallergic reactions: quantity and location of the drug on or in the skin; quantity, spectrum, and penetration capabilities of the activating radiation; thickness of the horny layer; degree of melanin pigmentation; and immunologic state of the affected person.^{17,18}

PHOTOSENSITIZERS

Photosensitizers are the chemicals that induce a photoreaction. The chemicals may be therapeutic, cosmetic, industrial, or agricultural. Most phototoxic reactions result from the systemic administration of the agent; photoallergic reactions may be caused by either topical or systemic administration of the agent. Many widely used medications are associated with photosensitivity reactions, but the frequency with which individual medication evokes this response is quite variable in the human population.^{1,8} The more commonly



used medications containing photoreactive agents include antibiotics (tetracyclines, fluoroquinolones, sulfonamides, etc.), nonsteroidal anti-inflammatory drugs (NSAIDs), cardiovascular drugs, diuretics, antidiabetic drugs, antidepressants, antipsychotics, antihistamines, skin agents, and others. A common adverse effect of several anti-infective agents and their derivatives is photosensitivity reactions. Most of them are cyclic and tricyclic hydrocarbons, frequently containing an alternative double-bond isoprene or naphthyridine nucleus. Fluoroquinolones, antibacterial agents, are well known to cause photosensitivity as an adverse effect. Empirical studies suggest pefloxacin and fleroxacin as the most potent photosensitizers while enoxacin, norfloxacin, and ofloxacin are less potent. Tetracyclines are example of the phototoxic hazards of antibiotics. Among them, chlorine derivatives most frequently cause phototoxicity. Sulfa-derived drugs (sulfonamide antibacterials, hypoglycemics, diuretics) have been well-known causes of photosensitivity reactions. Sunscreens help to reduce the effects of UVR, but some sunscreens contain ingredients that cause photosensitivity themselves. Among them, para-aminobenzoic acid (PABA) most frequently causes photosensitivity reactions; benzophenones are second in causing skin reactions. Usage of products containing photoreactive agents can aggravate existing skin diseases (eczema, herpes, etc.) and also precipitate or worsen autoimmune diseases.¹⁹

BIOPHYSICAL AND BIOCHEMICAL BACKGROUND

Ultraviolet (200-400 nm) and visible (400-800 nm) lights, to which the skin is continually exposed, are produced by the sun and artificial sources, such as tanning beds and fluorescent lamps. The UV spectrum is divided into 3 parts with arbitrary limits, i.e., UV-A (wavelength 320-400 nm), also called black light; UV-B or "sunburn" radiation (wavelength 290-320 nm) and UV-C (wavelength 200-290 nm). Of these wavelengths, only UV-A and UV-B are involved in photosensitivity reactions, since UV-C is blocked by the ozone layer of the atmosphere. Drug photosensitivity occurs in the skin in the presence of foreign molecules (exogenous chromophores), which absorb normally harmless doses of UV and visible radiation and create an electronically excited state. Absorbed photons from the electromagnetic spectrum are converted into chemical energy used in chemical reactions. These can transform the original chemical into a photoproduct, transfer the energy to a protein molecule, or shed the energy as either light or heat. Clinically, this process can result in erythema, edema, and sometimes blistering. Psoralens, nonsteroidal anti-inflammatory agents, phenothiazines, griseofulvin, sulfonamides, tetracyclines, nalidixic acid, and most fluoroquinolones react primarily with UV-A. A limited number of chemicals, for instance fleroxacin, depend mainly on UV-B activation. *In-vitro* photosensitivity requiring both UV-A and UV-B have been reported with the quinolones, oxolinic acid, pipemidic acid, rosoxacin,

and the newly developed fluoroquinolone sparfloxacin.^{20, 8}

The sunburn spectrum waves, UVB, are the prime factor in photoaging and photocarcinogenesis; UVA is primarily responsible for photosensitivity reactions because of its deeper penetration into the skin and contributes to phototrauma. UVB only penetrates into the epidermis and the papillary dermis, whereas UVA penetrates into the reticular dermis. UVB light does not penetrate window glass, whereas UVA light and visible light do. UVA rays do not vary in intensity with the time of day or the season in comparison to UVB. Photosensitivity reactions can occur in exposure to both UVA and UVB, but are more likely to occur in the UVA range. EMR travels in the form of waves containing photons. The absorption of photons of light is fundamental to phototoxicity and photoallergy. Absorption induces the movement of an electron to an outer unfilled electron shell and causes a condition known as an excited state. After this, one of two types of reaction occurs. In *phototoxic* reaction the photoactivated chemical cause direct cellular damage; no sensitization period is required, and mechanism is non-immunologic, so it can manifest during an initial exposure. The reaction is dependent upon the amount of the compound, level of activating radiation, and the quantity of other chromophores in the skin. Absorption of UVR produces an excited-state chemical or metabolite, which may in turn follow one of two pathways that lead to photosensitization. The first pathway proceeds through the generation of a free radical and the second pathway is through the generation of singlet oxygen, which in turn results in the oxidation of biomolecules, damaging critical cellular components and initiating the release of erythrocytic mediators.²¹

CLINICAL FEATURES AND DIAGNOSIS OF PHOTOTOXICITY AND PHOTOALLERGY

Individuals with phototoxic reactions may initially complain of a burning and stinging sensation. Then the redness typically occurs within 24 hours of the exposure to sun in the exposed areas of the body such as the forehead, nose, hands, arms, and lips. Individuals with photoallergic reactions may initially complain of pruritus. This is then followed by redness and possibly swelling and eruption of the involved area. Because this is considered an allergic reaction, there may be no symptoms for many days when the drug is taken for the first time. Subsequent exposure to the drug and the sun may cause a more rapid response in 1-2 days.



Table 1: Comparison of Features of Photosensitization Reactions

Feature	Phototoxic Reaction	Photoallergic Reaction
Occurrence	High	Low
Quantity of agent necessary for photosensitivity	Large	Small
Onset of reaction (after exposure to agent and light)	Few Minutes to hours	24-72 Hours
Whether more than one exposure to agent required	No	Yes
Immunologically mediation	No	Yes (Type IV)

Table 2: Common Photosensitizers and Their Phototoxic and Photoallergic reactions

Class	Medication	Phototoxic Reaction	Photoallergic Reaction
Antibiotics	Tetracyclines (doxycycline, tetracycline)	Yes	No
	Fluoroquinolones (ciprofloxacin, levofloxacin)	Yes	No
	Sulfonamides	Yes	No
Nonsteroidal anti-inflammatory drugs	Ibuprofen	Yes	No
	Ketoprofen	Yes	Yes
	Naproxen	Yes	No
	Celecoxib	No	Yes
Diuretics	Furosemide	Yes	No
	Bumetanide	No	No
	Hydrochlorothiazide	Yes	No
Hypoglycemics	Sulfonylureas (glipizide, glyburide)	No	Yes
HMG-CoA reductase inhibitors	Statins (atorvastatin, pravastatin, simvastatin)	Yes	Yes
Neuroleptic drugs	Phenothiazines (chlorpromazine, thioridazine)	Yes	Yes
	Thioxanthenes (chlorprothixene, thiothixene)	Yes	No
Antifungals	Terbinafine	No	No
	Itraconazole	Yes	Yes
	Voriconazole	Yes	No
	Griseofulvin	Yes	Yes
Other drugs	Para-aminobenzoic acid	Yes	Yes
	5-Fluorouracil	Yes	Yes
	Paclitaxel	Yes	No
	Amiodarone	Yes	No
	Diltiazem	Yes	No
	Quinidine	Yes	Yes
	Dapsone	No	Yes
Oral contraceptives	No	Yes	



Photosensitivity is a skin symptom that characterizes different groups of diseases, including specifically the photodermatoses where photosensitivity is the main clinical manifestation and also other disorders where photosensitivity is an associated symptom. Photodermatoses are classified into five general groups:

- (a) Idiopathic photodermatoses (polymorphic light eruption, actinic prurigo and solar urticaria);
- (b) Photodermatoses secondary to endogenous agents (mainly the porphyrias);
- (c) Photodermatoses which are secondary to exogenous agents (phototoxic and photoallergic reactions);
- (d) Photoexacerbated dermatoses (autoimmune disease, and nutritional deficiencies);
- (e) Genodermatoses.

Phototesting may be useful in evaluating photosensitivity to topical medications causing a photoallergic response. In cases of phototoxicity reactions, this test is generally not useful. In order to reveal an agent, template test sites are exposed to increasing doses of UVA (phototoxic reactions are almost due to UVA) while person is on the incriminated drug. The minimum dose of light required to produce uniform erythema over the entire irradiated site after 24 hours is called the minimum erythema dose (MED). The UVA MED will be much lower than that for normal individuals of the same skin phototype. After drug is excreted and then eliminated from the skin, a repeat of UVA phototest reveals an increase in the UVA MED. The usage of patch and *photopatch* tests (PPT) helps to diagnose photoallergic reactions. The indications for PPT are dermatitis predominantly affecting exposed sites with or without a history of a sunscreen reaction, chronic actinic dermatitis, and a photosensitive eruption for which there is no obvious diagnosis. Suspected photoallergens are applied to the back in two sets; one set is removed after 24 hours and irradiated with UVA of 5–10 J/cm². After 48 hours, both sets of patch tests are evaluated for a positive reaction; erythema, edema, and/or vesiculation at an irradiated site indicate a positive reaction. The occurred positive reaction at both sites is interpreted as an allergic contact dermatitis; the positive reaction at the unirradiated site with a stronger one at the irradiated site is interpreted as both allergic dermatitis and photoallergic contact dermatitis.²²

Phototesting with UV-A; UV-B; and, sometimes, visible light is helpful in diagnosing photosensitivity disorders. This test is performed by treating small areas of skin on the back or inner aspect of the forearms with gradually increasing doses of light. The minimum dose of light required to produce uniform erythema over the entire irradiated site after 24 hours is called the minimum erythema dose (MED). Patients with phototoxic reactions have a reduced MED to UV-A or, in some instances UV-B.²³

To date, no single method of assaying drug photosensitivity has emerged as the ideal yard stick for establishing photosensitivity. A panel of in vitro and in vivo assay systems has been established for studying photosensitivity reactions, which taken together have proven useful either to predict or to confirm the photosensitizing hazards of a new compound. Invitro methods used in preliminary screening for photosensitivity include measurement of UV and visible light absorption spectra of the drug; quantification of its ability to photo-oxidize histidine, to induce photohemolysis, and to inhibit yeast growth and mitogen-induced lymphocytic blast transformation; testing on skin equivalents; mutagenicity testing on different organisms and strains; and ability to bind to a protein carrier, such as serum albumin. Hairless mouse skin, guinea pig, albino mice, and rat auricular skin and retina are most commonly used for experimentally reproducing human skin response to drugs and UV exposure.²⁴

CONCLUSION

Drug photosensitization is a major problem since the abnormal reactions seriously limit or exclude the usage of drugs. The mainstays of treatment of drug-induced photosensitivity include identification and avoidance of the causative agent, the use of sun protection, and the institution of measures for symptomatic relief.

- (i) Topical steroid creams may be helpful in treating the redness, and antihistamines are generally helpful in minimizing the itching.
- (ii) The use of systemic corticosteroids should be reserved for the most severe cases.
- (iii) If sunscreens are not the cause of the photosensitivity, they should be used liberally.
- (iv) The sun protection factor (SPF) may not be a reliable indicator of protection against drug-induced photosensitivity. The SPF refers to the degree of protection against sunlight-induced sunburn, primarily that caused by UV-B. Most drug-induced photosensitivity reactions are caused by wavelengths within the UV-A range. Therefore, sunscreens that absorb UV-A should be prescribed.
- (v) Sunscreens that contain avobenzone, titanium dioxide, and zinc oxide are more effective in blocking out UV-A radiation than sunscreens that contain other ingredients.

Avoidance of direct sunlight, use of protective clothing and appropriate UV-A and UV-B sunscreens, and evening dosing strategy are factors that can minimize the risk of photosensitivity effects of most antimicrobials.



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