Scientific problems of photosensitivity

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Summary. *Photosensitive skin reactions occur when human skin reacts to ultraviolet radiation or visible light abnormally. The forms of photosensitivity are phototoxicity and photoallergy. Phototoxic disorders have a high incidence, whereas photoallergic reactions are much less frequent in human population. Several hundred substances, chemicals, or drugs may invoke phototoxic and photoallergic reactions. In order to avoid photosensitive reactions it is essential to determine the photosensitizing properties of such substances before drugs are introduced in therapy or products made available on the market. The article reviews the mechanisms of photosensitization, explains the most important differences between phototoxic and photoallergic reactions, summarizes the most common photosensitizers, and presents the clinical features and diagnostic procedures of phototoxic and photoallergic reactions.*

History of the problem

Photosensitive reactions have been recognized for thousands of years. In ancient Egypt, India, and Greece psoralen-containing plants extracts were combined with exposure to sunlight to treat skin diseases.

In 1897, reports of dermatitis following contact with parsnips and/or angelica came from both the United States and England, and in 1916, E. Freund observed characteristic hyperpigmented lesions that he attributed to eau de cologne containing bergamot oil (1). Unfortunately, none of the authors recognized the necessity of ultraviolet radiation (UVR) for the reaction.

In 1938, H. Kuske showed that plant furocoumarins caused photosensitization, and shortly thereafter, T. Jensen and K. G. Hansen reported that UVR between 320 and 380 nm caused the reaction maximum (1). In 1967, British researchers discovered that sandalwood oil in sunscreens and cosmetics caused photoallergies (2). Shortly thereafter, French scientists demonstrated that bergamot oil in sunscreens caused photosensitivity disorders, and German researchers isolated photoreactive agents from colognes, perfumes, and oral contraceptives (2).

Researchers published lists of photoreactive agents found in several hundred of substances, chemicals, and drugs. In order to avoid photosensitive reactions, scientists try to determine the photosensitizing properties of such substances before drugs are introduced in therapy or products made available on the market. In recent years research focuses on identifying what photoreactive agents could be found in products and how to prevent or control photosensitivity disorders.

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 (2). Photosensitivity reactions may be more specifically categorized as phototoxic or photoallergic in nature (2–5). Phototoxicity is much more common than photoallergy (2–7).

Photosensitivity reactions are hardly predictable. They can occur in persons of any age (4) but are more common in adults than children, possibly because adults are usually exposed to more medications and topical agents (5). The degree of photosensitivity varies among individuals; having the same impacts 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 (2).

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 (6), may influence the features of photosensitivity reactions. Person's immunological status is very important be-

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cause photosensitivity reactions are found frequently in immunocompromised human immunodeficiency virus (HIV)-infected patients (2, 6). If patient exhibits photodistributed skin problems of unknown origin, the possibility of HIV infection should be suspected.

Phototoxicity is a form of photosensitivity that is not depended on an immunologic response (3–8). 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 (5). Phototoxic reactions can appear on first exposure to the agent and demonstrate no cross-sensitivity to chemically related agents (5).

Photoallergy is a form of photosensitivity that is immunologically mediated (3–8). Photoallergic reactions develop only in sensitized persons (6–9) and are not dose dependent, although a sensitized person is likely to get a stronger reaction at a much higher dose (6). Chemically related agents via cross-sensitivity or cross-allergenicity may cause eruptions (5). In such cross-reaction, photosensitivity to one chemical increases a person's tendency for photosensitivity to the next chemical agent (2).

Photosensitizers

Photoreactive agents or photosensitizers are chemicals that induce a photoreaction. The chemicals may be therapeutic, cosmetic, industrial, or agricultural (10). Photosensitivity reactions can be caused by injected, oral, or topically applied chemical photosensitizers (2). In most cases, the mechanism is phototoxicity, but some agents cause photoallergy, and for some agents the mechanism is either uncertain, or both mechanisms may be involved (2, 6). 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 (4).

Everyday used items such as perfumes, soaps, deodorants, lotions, hair sprays and styling creams, artificial sweeteners, petroleum products, tattoos, and certain foods may contain photoreactive agents.

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. 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 (3, 4, 10). Some of the common drugs and their mechanisms of photodamage are listed in Table.

Topically applied photosensitizers, halogenated salicylanilides, benzocaine in soaps and other household products, or musk ambrette in aftershave lotions; and stilbenes in whiteners are the most frequent cause of photoallergic eruptions (10).

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 (6). Fluoroquinolones, antibacterial agents, are well known to cause photosensitivity as an adverse effect, and their cross-reactivity has been clinically documented (11). Empirical studies suggest pefloxacin and fleroxacin as the most potent photosensitizers while enoxacin, norfloxacin, and ofloxacin are less potent (6). Tetracyclines are example of the phototoxic hazards of antibiotics. Among them, chlorine derivatives most frequently cause phototoxicity (6).

Sulfa-derived drugs (sulfonamide antibacterials, hypoglycemics, diuretics) have been well-known causes of photosensitivity reactions since 1939 when S. Epstein first reported photoallergic contact dermatitis following intradermal injection of sulfanilamide (6).

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 (5).

Usage of products containing photoreactive agents can aggravate existing skin diseases (eczema, herpes, etc.) and also precipitate or worsen autoimmune diseases (lupus erythematosus, rheumatoid arthritis) (2).

Mechanisms of phototoxicity and photoallergy

The sunlight plays an important role in photobiological processes. However, the sunlight that has given us life can also cause significant morbidity in the form of sunburns, drug reactions, photosensitive diseases, and photoaging. Recurrent episodes of phototrauma over a lifetime can lead to the development of skin cancers.

Transformation of H to He in sun's interior liberates vast amounts of energy which reach the earth's surface in the form of electromagnetic radiation (EMR): x-rays, cosmic rays, electric waves, radio waves, infrared, visible light, and UVR (12). Photosensitivity reactions could be induced by a delimited range of the EMR spectrum that includes UVR (200–400 nm) and visible light (400–800 nm) (6). UVR

Table. **Common photosensitizing medications (adapted from A. Y. Zhang, C. A. Elmets (4))**

Class	Medication	Phototoxic reaction	Photoallergic reaction
Antibiotics	Fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin)	+	–
	Sulfonamides	+	–
	Tetracyclines (doxycycline, tetracycline)	+	–
Antihistamines	Promethazine	+	+
	Cyproheptadine	+	+
	Diphenhydramine	+	+
	Hydroxyzine	+	–
Antifungals	Itraconazole	+	+
	Voriconazole	+	–
Cardiovasculars	Amiodarone	+	–
	Diltiazem	+	–
	Quinidine	+	+
Diuretics	Furosemide	+	–
	Hydrochlorothiazide	+	+
Hypoglycemics	Sulfonylureas (glipizide, glyburide)	–	+
Neuroleptics	Phenothiazines (chlorpromazine, fluphenazine, perazine, perphenazine, thioridazine)	+	+
	Thioxanthenes (chlorprothixene, thiothixene)	+	–
Nonsteroidal antiinflammatory drugs (NSAIDs)	Celecoxib	–	+
	Ibuprofen	+	–
	Ketoprofen	+	+
	Naproxen	+	–
Retinoid	Acitretin	+	–
	Isotretinoin	+	–
Sunscreens	Benzophenones	–	+
	Cinnamates	–	+
	Para-aminobenzoic acid (PABA)	+	+
	Salicylates	–	+
Fragrances	Musk ambrette	–	+
	6-methylcoumarin	–	+

spectrum is divided into UVB=290–320 nm, UVA=320–400 nm (UVA II=320–340 nm and UVA I=340–400 nm), and UVC=200–290 nm (6, 9). Only UVA and UVB are involved in photosensitivity reactions because UVC is blocked by the ozone layer of the atmosphere (6, 9, 12).

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 (12). UVB only penetrates into the epidermis and the papillary dermis, whereas UVA penetrates into the reticular dermis (5, 12). UVB light does not penetrate window glass, whereas UVA

light and visible light do (4, 12). UVA rays do not vary in intensity with the time of day or the season in comparison to UVB (12).

Photosensitivity reactions can occur in exposure to both UVA and UVB, but are more likely to occur in the UVA range (2, 4, 5).

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 (13). After this, one of two types of reaction occurs.

In *phototoxic* reaction the photoactivated chemical cause direct cellular damage (4, 9); no sensitization period is required, and mechanism is non-immunologic (8), 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 (9).

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 erythrogenic mediators (9).

Photoallergic reaction may not be predicted. They are immunologically mediated and determined by either delayed hypersensitivity responses or, more rarely, immediate hypersensitive reactions due to IgE response to UVR (6). An incubation period for the immunologic memory to develop after the first contact with the photosensitizer is required, so there is no reaction on first exposure (8). On subsequent exposures, the elicitation of response is shorter (6).

The earliest evidence of an immune-mediated photosensitivity pathway arose from studies with 3,3',4',5-tetrachlorosalicylanilide, an allergic contact photosensitizing agent (9). The delayed type of photoallergy is more frequent. The pathogenetic mechanisms of photoallergic reactions are quite similar to allergic dermatitis: the photoantigen (hapten) is presented by epidermal Langerhans cells to T lymphocytes with all the subsequent features of delayed skin hypersensitivity response of lymphocytic infiltration, release of lymphokines, activation of mast cells, and increased cytokine expression (6).

It would be useful to determine the exact mechanism of a photosensitivity reaction because phototoxicity is dose dependent, and a decrease in dose or amount of radiation may help to minimize the reaction. Photoallergic reactions do not significantly change with alterations in these parameters. Unfortunately, several agents have both phototoxic and photoallergic mechanisms, and it may be clinically difficult to differentiate between the two types of reactions.

Clinical features and diagnosis of phototoxicity and photoallergy

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 (14). Photodermatoses are classified into five general groups:

- idiopathic photodermatoses (polymorphic light eruption, actinic prurigo, hydroa vacciniforme, chronic actinic dermatitis, and solar urticaria);
- photodermatoses which are secondary to exogenous agents (phototoxic and photoallergic reactions);
- photodermatoses secondary to endogenous agents (mainly the porphyrias);
- photoexacerbated dermatoses (autoimmune disease, infectious conditions, and nutritional deficiencies);
- genodermatoses (15).

The directed personal and family history, morphology of the eruption, histological, immunological, biochemical findings, phototests, in some patients photopatch tests are important in focusing the diagnosis.

Both phototoxic and photoallergic reactions occur in sun-exposed areas of skin, including the face, neck, and dorsal surfaces of the hands and forearms, but the hair-bearing scalp, postauricular and periorbital areas, and submental portion of the chin are usually spared (4). Photosensitive reaction can fluctuate from mild to chronic depending on the sensitivity of the individual. Localized eruption indicates a reaction to a locally applied topical photosensitizer, whereas a widespread eruption indicates exposure to a systemic photosensitizer.

Acute *phototoxic* reaction usually has a rapid onset and presents as an exaggerated sunburn reaction with erythema and edema that occurs within minutes to hours of light exposure (4, 7) with intensity increasing in a dose-dependent manner (6). Vesicles may develop in severe reactions (4). Symptoms usually peak 24 to 48 hours after initial exposure (7). The most important clinical sign is that symptoms occur only on the areas of the skin exposed to sunlight (5, 7). Clinical improvement often occurs within 48 to 96 hours (7), and

the lesions often heal with hyperpigmentation (4).

A less common skin manifestation of phototoxicity is pigmentary changes: a blue-gray pigmentation is associated with amiodarone, chlorpromazine, and some tricyclic antidepressants; a brownish discoloration is associated with psoralen-containing botanicals and drugs (4). Photosensitizing drugs may also cause a lichen planus-like eruption and pseudoporphyria in sun-exposed areas (4).

The phototoxic effect of some drugs (tetracycline, psoralen, chloramphenicol, fluoroquinolones, oral contraceptives, quinine, mercaptopurine) on nails is a well-known phenomenon referred to as photo-onycholysis; it may be the only manifestation of photosensitivity (4, 6, 16).

Histologically, phototoxicity is characterized by dermal edema, dyskeratosis, and necrosis of the keratinocytes (7). In case of severe reaction, the necrosis is panepidermal (4). Epidermal spongiosis with dermal edema and a mixed infiltrate consisting of lymphocytes, macrophages, and neutrophils may be present (4).

Photoallergic reactions primarily occur on the areas of the skin that are exposed to UVR but may spread beyond these to other areas (5, 12). According to the model of administration of the photosensitizer, photoallergic reactions can be contact photoallergic dermatitis or photoallergy induced by systemic agents.

The onset of a photoallergic reaction is usually delayed for 24 hours or even several days, and recovery is often slower than from a phototoxic reaction, with the reaction sometimes persisting for some time after the offending product has been discontinued (5). This reaction presents as an eczematous eruption with erythema, papules and vesicles, pruritis, weeping, oozing and crusting, and later, scaling and lichenification (5). Hyperpigmentation does not occur in photoallergic reactions (4). Photoallergic reactions may also be macular, bullous, or acute urticarial lesions and may develop within minutes after exposure to UVR (5).

Histologically photoallergic reaction is similar to contact dermatitis. Epidermal spongiosis with a dermal lymphocytic infiltrate is a prominent feature (4, 7). The presence of necrotic keratinocytes is suggestive of photoallergy rather than allergic contact dermatitis (4).

Phototesting. 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 (10). 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) (4). 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 (10).

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 (17).

The list of agents used for photopatch tests varies greatly among countries. Over the past years, a review of the relevant allergens for photopatch testing shows that virtually all positive photopatch tests are because of sunscreen ingredients (18). In resent years photopatch testing has focused on organic sunscreens and also include testing with each patient's own suspected products (17). Previous photoallergens such as 6-methyl coumarin and musk ambrette have been discontinued by the perfume industry in Europe because of previous frequent sensitization (18).

PPT should not be done when the skin test area is active. In order to avoid the effects of the angry back syndrome it is recommended that PPT should be made on skin that has been clinically normal for the previous two weeks (17). 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/cm^2. 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 (4). Photopatch tests are done in duplicate because photoallergens also can cause contact hypersensitivity (10). 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 (4).

Conclusions

1. The prevalence of photosensitivity in the general population is uncertain. There is a need for randomized, controlled trials of strategies for prevention, control, and treatment of photosensitivity disorders.

2. Additional data are needed for a better assessment of the risk of photosensitivity that is associated with many drugs. Drug photosensibilization is a major problem since the abnormal reactions seriously limit or exclude the usage of drugs.

3. The photobiological risk associated with the use of drugs depends on environmental and individual

factors. If the photosensitizing effect of a chemical or drug is known before patient's exposure, appropriate clinical management may help to control the photosensitivity reactions. Sunlight protection often prevents photosensitivity reactions. Avoidance of direct sunlight and sun-tanning facilities, usage of protective clothing and appropriate sunscreen (if it is not the offending agent), and evening dosing strategy are factors that can minimize the risk of photosensitivity effects of most drugs. Such patients should be warned against the use of tanning beds and about cross-reactions of the offending drug.

4. Sometimes photosensitivity can be useful for medicine and science. Photodynamic therapy is a treatment that uses a drug, photosensitizer, and a particular type of light. Photodynamic therapy involves the use of photochemical reactions mediated through the interaction of photosensitizing agents, light, and oxygen for the treatment of malignant or benign diseases.

Mokslinės fotojautrumo problemos

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Raktažodžiai: fotojautrumas, fotosensibilizatoriai, fototoksinė reakcija, fotoalerginė reakcija.

Santrauka. Fotojautrumo reakcijų atsiranda tada, kai žmogaus oda nenormaliai reaguoja į ultravioletinį spinduliavimą arba matomą šviesą. Fototoksinės ir fotoalerginės reakcijos gali būti sukeltos keleto šimtų įvairiausių medžiagų, chemikalų ar vaistų. Norint išvengti tokių reakcijų, būtina nustatyti medžiagų fotosensibilizuojančias savybes iki tol, kai jos bus taikomos gydymui arba naudojamos buityje. Fototoksinės reakcijos yra dažnesnės nei fotoalerginės. Šiame straipsnyje analizuojami fotosensibilizacijos mechanizmai ir pabrėžiami svarbiausi skirtumai tarp fototoksinių ir fotoalerginių reakcijų, aprašomi dažniausi fotosensibilizatoriai, klinikinės ir diagnostinės fototoksinių ir fotoalerginių reakcijų ypatybės.

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