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Phototoxic and Photoallergic Skin Reactions

Liborija Lugović, Mirna Šitum, Suzana Ožanić-Bulić and Ines Sjerobabski-Masnec

Department of Dermatology and Venereology, University Hospital »Sestre milosrdnice«, Zagreb, Croatia

A B S T R A C T

Indirect action of sun together with different exogenous agents (systemic medications and topically applied compounds) sometimes may result in phototoxicic and photoallergic reactions. Drug-induced photosensitivity reactions refer to the development of cutaneous disease as a result of the combined effects of a drug and light (mostly spectrum within the UVA and visible light range or UVB range). The aim of the review was to show the prominent features of phototoxic and photoallergic reactions, which occur in sun-exposed areas, including face, neck, hands and forearms. Phototoxic reactions are significantly more common than photoallergic reactions and mosty resemble to exaggerated sunburn. Photoallergic reactions appear only in a minority of individuals and resemble allergic contact dermatitis on sun-exposed areas, although sometimes may extend into covered areas. Generally, the physical examination and a positive patient's history of photosensitivity reactions on substances are of great importance for the diagnostics. The treatment of these reactions includes identification and avoidance of offending agent and application of anti-inflammatory dressings, ointments and corticosteroids.

***Key words**: photosensitivity, phototoxic, photoallergic reactions*

Introduction

Following sun exposure, because of a direct damage of skin by UV radiation, cutaneous changes appear in the form of sunburn or other sun induced dermatoses. Long-term effects of sun damage include degenerative and malignant skin disorders, as well as, solar elastosis and skin tumours. Indirect action of sun together with different exogenous agents results in phototoxicity and photoallergy[1,2]. Drug-induced photosensitivity refers to the development of cutaneous disease as a result of the combined effects of a chemical agent and light[1]. Therefore photoactivation of the chemical agent may cause phototoxic and photoallergic cutaneous reactions (table 1). Drug-induced photosensitivity reactions are mostly stimulated by action spectrum within the UVA (320–400 nm) and visible light range or sometimes UVB (290–320 nm) range. Photosensitivity reactions, phototoxic and photoallergic, may be result of systemic medications and topically applied compounds. There are many potential exogenous agents causing photosensitivity reactions (table 2)[1,2]. Although, sometimes the two can not be distinguished on the clinical basis, there are a number of distinguishing characteristics (table 1).

Both phototoxic and photoallergic reactions occur in sun-exposed areas, including face, neck, hands and forearms, with the exception of hair-bearing scalp, retroauricular and periorbital areas, and submental part of the chin growth[4]. A widespread eruption suggests exposure to a systemic photosensitizer, whereas a localized eruption indicates a reaction to a topical photosensitizer. Sometimes phototoxic reactions are of a benefit for a patient, e.g. psoralens and tar containing products which, after applying to the skin after the UV exposure cause specific photosensitivity reaction, and by increasing cell turnover influence the disease course acting as therapeutic agents[5].

Phototoxic Reactions in the Skin

Phototoxic reactions occur because of the damaging effects of light-activated cell membrane compounds and DNA. These reactions are more common in individuals exposed to sufficient amounts of light and an exogenous agent, and usually appear as an exaggerated sunburn re-

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TABLE 1
DISTINGUISHING CHARACTERISTICS OF PHOTOTOXIC AND PHOTOALLERGIC REACTIONS

Feature	Phototoxic reaction	Photoallergic reaction
Incidence	High (more common)	Low (less common)
Amount of agent required for photosensitivity	Large	Small
Mechanisms	No immune reactions, light-activated cell membrane compounds and DNA	Immunologically mediated cell-mediated immune responses (type IV) to a light-activated compound
Onset of reaction after exposure to agent and light	Minutes to hours	24–72 hours
Distribution	Sun-exposed skin only	Sun-exposed skin, may spread to unexposed areas
Clinical characteristics	Exaggerated sunburn	Dermatitis, photoallergen applied topically eczematous morphology; photoallergen systemically drug eruption

sponse. Phototoxic reactions result from direct tissue damage caused by a photo-activated compound. Many compounds have the potential to cause phototoxicity and have at least one resonating double bond or an aromatic ring that can absorb radiation energy. The most common causative agents are furocoumarins, acridinic dyes or eosine. Some drugs are more phototoxic, for example, phenothiazines, tetracycilnes, sulfonamides, amiodarone, dacarbazine, etc.[6,7]. Phototoxic dermatitis is inflammatory skin reaction caused exclusively by photochemical reaction (without immunologic mechanisms), leading to the toxic reaction of various chemicals activated by UV light and action on cell membrane components, e.g. DNA[2]. Most compounds are activated by wavelengths within the UVA range, although some compounds have peak absorption within the UVB or visible light range. The reactive compound absorbs and transmits energy creating oxygen free radicals, superoxide anions, hydroxyl radicals and heat therefore damaging the cells in phototoxic way metastasis[8]. The complex mechanism of cell damage comprises complex of different reactions. In most instances, photoactivation of a compound results in the activation of electrons from the stable singlet state to an excited triplet state. As activated electrons return to a more stable configuration, they transfer their energy to oxygen, leading to the formation of reactive oxygen intermediates, such as singlet oxygen, superoxide anions, and hydrogen peroxide leading to damage of cell membranes and DNA. This includes the signal transduction pathways that result in the production of pro-inflammatory cytokines and arachidonic acid metabolites, the main components of inflammatory response, resembling an exaggerated sunburn reaction load[2]. Another form of drug-induced phototoxicity is psoralen-induced phototoxicity, where psoralens intercalate within DNA, forming monofunctional adducts and, after exposure to UVA radiation, bifunctional adducts within DNA. It is still not known how bifunctional adducts cause photosensitivity. As a result of described reaction on photoexposed body areas the inflammatory reaction occurs in the form of acute dermatitis characterized by erythema, oedema, blisters and secondary hyperpigmentation[1,2]. Phototoxic responses often occur within minutes to hours of sun exposure, appearing earlier than photoallergic reactions. Acute phototoxicity often begins as an exaggerated sunburn reaction (erythema and oedema) within minutes to hours of sun exposure, while in severe cases vesicles and bullae are also seen. The lesions often heal with secondary hyperpigmentation, resolving in a matter of weeks to months. Chronic phototoxicity may appear as an exaggerated sunburn reaction or lichenification, caused by repeated rubbing and scratching. Thus, distinguishing phototoxic from photoallergic reactions strictly on physical appearance of the lesions may be difficult[1]. Other less common skin manifestations of phototoxicity include pigmentary changes, such as blue-grey pigmentation associated with several agents, including amiodarone, chlorpromazine, and some tricyclic antidepressants. Reactions to psoralen-containing plants (e.g. phytophotodermatitis) and drugs may also resolve with a brownish discoloration. Photosensitizing drugs may, as well, cause a lichen planus–like eruption in sun-exposed areas, such as reaction to demeclocycline, hydrochlorothiazide, enalapril, quinine, quinidine, chloroquine, and hydroxychloroquine patients[10]. Sometimes photosensitizing drugs may also cause pseudoporphyria, with porphyria cutanea tarda-like changes, characterized by skin fragility and subepidermal blisters on the dorsal part of hands, e.g. after exposure to naproxen, nalidixic acid, tetracycline, sulfonylureas, furosemide, dapsone, amiodarone, etc patients[11,12]. Treatment of patient with severe phototoxic reactions includes management of skin changes in burn care units, with application of anti-inflammatory dressings, ointments and corticosteroids (e.g. creams, emulsions) and the most important identification and avoidance of any offending agent.

Forms of Phototoxic Reactions

Berloque dermatitis is another form of phototoxic reaction resulting from the local application of various cosmetical compounds and UV light (mostly UVA). In most instances it results from the application of cosmetical products (after-shave, soaps, creams, etc.), which contain phototoxic substances (e.g. oleum bergamote). Described phototoxic reaction appears on photoexposed body parts in the form of erythema, oedema, vesicles and bullae with long lasting residual hyperpigmentations. The most common sites are the face, neck and neckline. Treatment includes complete avoidance of cosmetical compounds containing photosensitising substances. The resulting hyperpigmentation can be treated with 5% to 10% monobenzil esther of hydrokinone or with 0.15% A-vitamin acid patients[2]. Phytophotodermatitis is a form of photoreaction resulting in toxic dermatitis after the contact with plants on photo exposed body areas after sun exposure[2,9]. Furocoumarins from plants together with UVA induce acute bullous reaction with erythema and postinflammatory hyperpigmentations. The treatment comprises of local application of different antibacterial and corticosteroid creams and lotions. Photo-onycholysis may also be a manifestation of phototoxicity, mostly induced by the use of systemic medications, in-

TABLE 2
COMMON PHOTOSENSITIZING MEDICATIONS

Class	Medication	Phototoxic Reaction	Photoallergic Reaction
Antibiotics	Tetracyclines (doxycycline, tetracycline)	Yes	No
	Fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin)	Yes	No
	Sulfonamides	Yes	No
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Ibuprofen	Yes	No
	Ketoprofen	Yes	Yes
Diuretics	Furosemide	Yes	No
	Hydrochlorothiazide	Yes	Yes
Retinoids	Isotretinoin	Yes	No
	Acitretin	Yes	No
Hypoglycemics	Sulfonylureas (glipizide, glyburide)	No	Yes
PDT Pro-photosensitizers	5-aminolevulinic acid	Yes	No
	Methyl-5-aminolevulinic acid	Yes	No
	Verteporfin	Yes	No
	Photofrin	Yes	No
Neuroleptic drugs	Phenothiazines (chlorpromazine, fluphenazine, perazine, perphenazine, thioridazine)	Yes	Yes
	Thioxanthenes (chlorprothixene, thiothixene)	Yes	No
Antifungals	Itraconazole	Yes	Yes
	Voriconazole	Yes	No
Sunscreens	Para-aminobenzoic acid (PABA)	No	Yes
	Cinnamates	No	Yes
	Benzophenones	No	Yes
	Salicylates	No	Yes
Fragrances	Musk ambrette	No	Yes
	6-Methylcoumarin	No	Yes
Other drugs	Para-aminobenzoic acid (PABA)	Yes	Yes
	5-FU	Yes	Yes
	Amiodarone	Yes	No
	Diltiazem	Yes	No
	Quinidine	Yes	Yes
	Coal tar	Yes	No
	Dapsone	No	Yes

cluding tetracycline, psoralens, chloramphenicol, fluoroquinolones, oral contraceptives, quinine, and mercaptopurine.

Photoallergic Reactions in The Skin

Photoallergic reactions are less prevalent and develop only in a minority of individuals exposed to the combination a compound (mostly systemic drugs) and UV light. Photoallergic reactions can be caused either by topical or systemic administered substance. The amount of drug required for photoallergic reactions is considerably smaller than that required for phototoxic reactions. Photoallergic reactions resemble allergic contact dermatitis, with a distribution limited to sun-exposed areas, although they may sometimes extend into covered areas of skin[3,7]. Described reactions are cell-mediated immune responses to a light-activated compound and typically develops in sensitized individuals 24–48 hours after exposure. The antigen is a light-activated drug transformed to a metabolite that binds to protein carriers in the skin forming a complete antigen. The reaction then proceeds exactly as other cell-mediated immune responses do. Specifically, Langerhans cells (LCs) and other antigen-presenting cells take up the photoallergen and migrate to regional lymph nodes where present it to T cells, which express antigen-specific receptors. Then T cells become activated, proliferate, and return to the site of photoallergen deposition, leading to an inflammatory skin response[2]. Generally, when the photoallergen is applied topically there is usually an eczematous response, but if the photoallergen is administered systemically, the result is a skin drug reaction. The reaction usually manifests as a pruritic eczematous eruption with erythema and vesicles in the acute phase, while more chronic exposure results in erythema, lichenification and scaling. Hyperpigmentation does not occur in photoallergic reactions. Photoallergic reactions are significantly less common than phototoxic reactions, still with unknown frequency. Men are more likely to have photoallergic reactions than women. Generally, drug-induced photosensitivity reactions can occur in persons of any age[2]. The carcinogenic potential due to prolonged exposure to photosensitizing drugs has been suggested.

Diagnostics

The physical examination and a positive patient's history of photosensitivity reactions on medications or substances locally applied to the skin are of great importance (e.g. sunscreens, fragrances, antibacterial soaps, etc.). In the diagnosis of photoallergic contact dermatitis, photopatch testing is an important tool, performed by applying suspected photoallergens to the back in 2 sets (one set is removed after 24 hours and irradiated, and both sets of patch tests are evaluated for a positive reaction (manifested with erythema, oedema, and/or vesicles after 48 hours)[14,15]. A positive reaction at the non-irradiated site with a stronger one at the irradiated site should be interpreted as both allergic dermatitis and photoallergic contact dermatitis reaction to the same compound[2,14]. Phototesting with UVA, UVB, and in some instances, visible light is helpful in diagnosing photosensitivity disorders and performed by exposing small areas of skin on the back or inner aspect of the forearms with gradually increasing doses of light. Histopathologic analysis of phototoxic reactions shows epidermal spongiosis and dermal oedema, with mixed infiltrate of lymphocytes, macrophages, and neutrophils. In acute phototoxic reactions, necrotic keratinocytes are observed. Blue-grey pigmentation is characterized by phototoxic reactions results from increased melanin in the dermis or deposition of the drug or its metabolites in the skin[2]. Photoallergic reactions histologically resemble contact dermatitis, with epidermal spongiosis and dermal lymphocytic infiltrate, necrotic keratinocytes, which is suggestive of photoallergy.

Therapy

Treatment of photodermatoses includes identification and avoidance of the causative agent, symptomatic measures, topical corticosteroids, cool dressings, and systemic corticosteroids in the severe cases. If sunscreens are not the causative agents, patients are encouraged to use the sunscreens with UVA protection. SPF is not a reliable indicator of protection against drug-induced photosensitivity and refers to the degree of protection against primarily UVB range.

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L. Lugović

Clinical Department of Dermatovenerology, University Hospital »Sestre milosrdnice«, Vinogradska cesta 29, 10000 Zagreb, Croatia
e-mail: liborija@yahoo.com

FOTOKSIČNE I FOTOALERGIJSKE KOŽNE REAKCIJE

S A Ž E T A K

Indirektno djelovanje sunca zajedno sa različitim egzogenim tvarima (sistemski lijekovi i lokalno aplicirane tvari) ponekad mogu dovesti do fototoksičnih i fotoalergijskih reakcija. Fotopreosjetivost potaknuta lijekom odnosi se na razvoj kožne bolesti kao rezultat kombiniranog djelovanja lijeka i svjetla (većinom unutar UVA spektra i vidljivog svjetla ili UVB). Cilj ove studije bio je prikazati istaknute karakteristike fototoksičnih i fotoalergijskih reakcija koje se odvijaju na fotoeksponiranim predjelima, uključujući lice, vrat, šake i podlaktice. Fototoksične reakcije su značajno učestalije od fotoalergijskih reakcija i većinom sliče teškim opekotinama. Fotoalergijske reakcije se javljaju samo u malog broja ljudi i sliče alergijskom kontaktnom dermatitisu na fotoeksponiranim predjelima, iako se ponekad mogu širiti na neizložene dijelove. Općenito su od velikog značenja za dijagnozu bolesnika s reakcijom preosjetljivosti na različite tvari fizikalni pregled i pozitivna anamneza. Liječenje ovih reakcija uključuje prepoznavanje i izbjegavanja takvih tvari te primjenu antiupalnih krema, masti i kortikosteroida.