Clinics in Dermatology (2014) **32**, 73–79

ELSEVIER

Clinics in Dermatology

Photodermatoses, including phototoxic and photoallergic reactions (internal and external)

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Abstract Photodermatoses are caused by an abnormal reaction mainly to the ultraviolet component of sunlight. Photodermatoses can be broadly classified into four groups: immunologically mediated photodermatoses, chemical- and drug-induced photosensitivity, photoaggravated dermatoses, and DNA repair-deficiency photodermatoses. In this review, we focus mainly on chemical- and drug-induced photosensitivity, namely, phototoxicity and photoallergy.

Photosensitivity can be caused by many different topical or systemic exogenous agents. These agents are usually compounds with unsaturated double bonds, which absorb ultraviolet A wavelength energy. Drugs and chemicals that are most frequently responsible for phototoxic and photoallergic reactions will be discussed briefly. Pathophysiology, clinical manifestations, and histopathologic investigations of both phototoxicity and photoallergy are summarized separately. The main differences between these two entities, including clinical appearance, pathophysiologic mechanisms, and time of onset, will be emphasized.

Photosensitivity is a challenging area of dermatology, with a wide range of morbidities, both for the physician and the patient. For the exact diagnosis and precise control of photosensitivity, a systematic approach is vital. Avoidance of direct sunlight and sun-tanning facilities, as well as photosensitizing agents, usage of clothing with ultraviolet filters, and appropriate sunscreen can all minimize the risk for photosensitivity effects. A combination of measures, including phototherapy in different modalities and topical and systemic drugs, can be beneficial in the management of photodermatoses.

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0738-081X/$ – see front matter © 2014 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.clindermatol.2013.05.027

Introduction

Photodermatoses can be broadly classified into four groups: immunologically mediated photodermatoses, chemical- and drug-induced photosensitivity, photoaggravated dermatoses, and inherited disorders with defective DNA repair or with chromosomal instability.[1] Immunologically mediated photodermatoses are solar urticaria, polymorphous light eruption, hydroa vacciniforme, actinic prurigo, and chronic actinic dermatitis.[2] This large group of diseases is also called *primary idiopathic photodermatoses*, because these diseases consist of ultraviolet (UV)-induced cutaneous lesions with an unknown cause. Chemical- and drug-induced photosensitivity can be caused by topical or systemic exogenous agents, as is the case in phototoxicity and photoallergy; these reactions can also be caused by endogenous agents like in cutaneous porphyrias and pellagra.[1] Photoaggravated dermatoses, or so-called secondary photodermatoses, are the result of increased sensitivity to UV radiation caused by the underlying disease. Acne vulgaris, atopic dermatitis, bullous pemphigoid, carcinoid syndrome, cutaneous T-cell lymphoma, Darier disease, dermatomyositis, disseminated superficial actinic porokeratosis, erythema multiforme, Grover disease, lichen planus, lupus erythematosus, pemphigus, pityriasis rubra pilaris,

psoriasis, reticular erythematous mucinosis, rosacea, seborrheic dermatitis, and viral infections are examples of photoaggravated dermatoses.[1,2]

Inherited disorders with defective DNA repair mechanisms or with chromosomal instability can be listed as ataxia-telangiectasia, Bloom syndrome, Cockayne syndrome, Hailey-Hailey disease, Hartnup disease, Kindler syndrome, Rothmund-Thomson syndrome, trichothiodystrophy, and xeroderma pigmentosum.[3]

Photosensitivity is the reaction of skin to exogenous or endogenous agents.[4] These agents are usually compounds with unsaturated double bonds, which absorb ultraviolet A (UVA) wavelength energy. Exogenous agents can be used systemically or topically, and cutaneous porphyrias are examples of photosensitivity induced by endogenous agents.[5]

Photosensitivity induced by exogenous agents is classified into two groups: phototoxicity and photoallergy (Table 1). Phototoxicity is a direct tissue injury, caused by phototoxic agent and radiation, which can be seen in every individual. In contrast, photoallergy is a delayed-type hypersensitivity reaction. It is caused by chemicals that are modified by absorbing photon energy. It does not occur during the first exposure and has a sensitization phase.

The incidence of photosensitivity is rather low, and phototoxic reactions are far more common than photoallergic reactions.[2] The prevalence of exogenous drug-induced photosensitivity is not known, but data from photodermatology referral centers show 7% to 15% for phototoxicity and 4% to 8% for photoallergy.[6] In studies performed in the United States and Europe, the incidence rate of photoallergic contact dermatitis in patients who are photopatch-tested is between 1.4% to 12.0%.

Age distribution is rather homogeneous, but for drug-induced photosensitivity, the elderly population is more susceptible.[6]

More than 300 types of medications are responsible for photosensitivity.[7] Among topical phototoxic agents, the most commonly used ones are fluorescein, fluorouracil, furocoumarins, retinoids, rose bengal, and tar. For systemic phototoxic agents, the list is much longer. Many antifungals such as griseofulvin; antimalarials such as chloroquine and quinine; antimicrobials such as sulfonamides, tetracyclines, trimethoprim, quinolones, amiodarone, and quinidine; and diuretics such as furosemide, thiazides, psoralens, and sulfonylureas can cause phototoxic reactions. The photoallergic chemicals can also be classified into topical and systemic agents. Topical agents refer mostly to sunscreen ingredients, such as benzophenones, para-aminobenzoic acid (PABA) derivatives, cinnamates, and fragrance chemicals (methyl coumarins, musk ambrette, and sandalwood oil). Surface disinfectants, skin cleansers such as chlorhexidine, hexachlorophene, pesticides, and topical nonsteroidal anti-inflammatory agents are also topical agents. Systemic photoallergens can be listed as griseofulvin, quinolone, quinine, ketoprofen, and pyridoxine.[8]

Phototoxicity

Pathophysiology

More than one mechanism is usually involved in the pathophysiology of phototoxicity. A photosensitizer chemical absorbs UVA radiation energy. Before this absorption, the substance being at its ground state rises to an excited state molecule, with the effect of UV energy. This excited state chemical is involved in oxygen-dependent reactions, and at the end of these reactions cytotoxic injury is observed. These pathways of reactions can be studied in two major classes: type 1 and 2 reactions.[7]

During type 1 reactions, an electron is transferred to the excited state photo sensitizer, and this reaction results in free radical formation. These free radicals are involved in oxidation-reduction reactions and occurring peroxides cause cell damage.[9]

Type 2 reactions are, in contrast, energy transfer processes. Here again, transfer of energy to ground state oxygen causes oxygen radical formation. These radicals interact with unsaturated fatty acids, and in the end,

Table 1 Differences and similarities between phototoxicity and photoallergy

	Phototoxicity	Photoallergy
Clinical presentation	Sunburnlike reaction, erythema, edema with vesicles and bullae	Pruritic eczematous lesions
Pathophysiology	Direct tissue injury	Type IV delayed hypersensitivity
Histology	Epidermal necrosis, dermal edema with eosinophilic keratinocytes, dermal infiltrate of lymphocytes, macrophages, and neutrophiles	Spongiotic dermatitis, dermal lymphohistiocytic infiltrate
Onset and occurrence	Occurs after first exposure and starts minutes to hours after exposure	No reaction after first exposure, starts 24-48 hours after exposure
Dose	Large doses needed	Small doses are enough
Cross-reactivity	None	Common
Diagnosis	Clinical and phototests	Clinical and photopatch tests