Clinics in Dermatology (2016) **34**, 571–581

ELSEVIER

Clinics in Dermatology

Drug-induced photosensitivity: Photoallergic and phototoxic reactions

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Abstract Drug-induced photosensitivity refers to the development of cutaneous disease due to the interaction between a given chemical agent and sunlight. Photosensitivity reactions can be classified as phototoxic or photoallergic. Sometimes, there is an overlap between these two patterns, making their distinction particularly difficult for the clinician. We review the drugs that have been implicated as photosensitizers, the involved mechanism, and their clinical presentations. The main topical agents that cause contact photosensitivity are the nonsteroidal antiinflammatory drugs, whereas the main systemic drugs inducing photosensitivity are antimicrobials, nonsteroidal antiinflammatory agents, and cardiovascular drugs. Drug-induced photosensitivity remains a common clinical problem and is often underdiagnosed.

Introduction

Drug-induced photosensitivity refers to the development of a cutaneous disease due to exposure to a chemical agent and sunlight.[1] The chemical agent can be a topical or systemic drug able to reach the skin. Drug-induced photosensitivity commonly occurs in clinical practice, representing up to 8% of reported cutaneous adverse events from drugs.[2] Many drugs, including several classes of antimicrobials, nonsteroidal antiinflammatory drugs (NSAIDs), cardiovascular agents, and even psychotropics have been implicated in photosensitive reactions.

Data suggest that more than 300 drugs are reported to be photosensitizers; however, most of the time the relationship between the drug and sun exposure may not be obvious and the effect of only a few drugs have been well described.[3] This leads to numerous underdiagnosed and underreported reactions. It is important to establish this relationship to remove the offending agent or take adequate measures to prevent adverse effects.

Photosensitive drugs are exogenous chromophores that absorb photons. They are activated on sun exposure and undergo chemical reactions.[3] The chemical structure of a chromophore determines the wavelengths of radiation that it absorbs. Most photosensitive reactions are caused by ultraviolet A (UVA) rather than ultraviolet B (UVB) radiation.[4] Depending on the pathophysiologic mechanism, ultraviolet radiation (UVR) can induce an inflammatory reaction (phototoxicity) or a T-cell–mediated reaction (photoallergy).[3]

In an effort to distinguish between both identities, clinical history, physical examination, histologic examination, and some tests such as phototesting and photopatch testing may be used; however, the distinction can be difficult and most drugs can induce both pathophysiologic patterns.

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http://dx.doi.org/10.1016/j.clindermatol.2016.05.006
0738-081X/

Photosensitive drug reaction: Phototoxicity versus photoallergy

On physical examination of a patient with a photosensitive drug reaction, one expects to see a photodistribution classically involving the face, neck, forearms, and hands, while sparing non–sun-exposed areas, including the breasts and genitalia.[5]

Clinical manifestations of photosensitivity can include the classic pruritic eczematous eruption of photoallergy and the typical exaggerated sunburn eruption of phototoxicity. Several other manifestations are possible, such as lichenoid eruptions, onycholysis, erythema multiforme, hyperpigmentation, telangiectasia, and even pseudoporphyria in the absence of abnormal porphyrin levels.[5]

A distinction between the two patterns of photosensitivity, photoallergic and phototoxic reactions, may be difficult, but some principles have been established. Photoallergic drug reactions are less common than phototoxic reactions and usually require a minimal exposure to the photosensitizing drugs and prior sensitization.[6] The mechanism is immunologically mediated, a photoproduct acts as a hapten or as a complete antigen to generate a type IV hypersensitivity reaction, and cross-reactions between similar drugs can occur.[4] Usually, it develops 24 hours or more after the initial exposure, and it resembles an eczematous dermatitis that may spread beyond the sun-exposed skin. After discontinuation, the photoallergy resolves; however, in rare cases it can persist and evolve into chronic actinic dermatitis.[6] Histologically, epidermal spongiosis, vesiculation, exocytosis of lymphocytes into the epidermis, and perivascular inflammatory infiltrates are seen. Prior contact with the drug may not be necessary if the patient has previously been sensitized by contact with a similar molecule.[4]

Phototoxic drug reactions, besides happening much more often, will supposedly occur in all individuals exposed to high enough doses of either the drug or the radiation at the appropriate wavelengths.[5] The phototoxic reaction is the result of direct tissue and cellular injury by a photoproduct.[4] Usually, it is dose dependent and does not require prior sensitization.[6] It occurs minutes to hours after sunlight exposure and manifests clinically as exaggerated sunburn with associated burning and itching sensations localized on sun-exposed areas. Histologically, this reaction displays epidermal keratinocytes necrosis with dermal lymphocytic and neutrophilic infiltrate.[5]

In clinical practice, the two testing methods that have proven useful to differentiate the photosensitive mechanism are phototesting and photopatch testing.

Phototesting involves the use of a solar simulator with the aim to determine whether the minimal erythema dose (MED; exposure to UVR leading to the first faint reddening of the skin) is reduced in the presence of the agent. It is done in a number of shielded and unshielded areas on the upper back of the patient while taking and then not taking the suspected drug.[5]

Photopatch testing is indicated for the evaluation of photoallergy.[6] It involves the application of drugs on the patient's back and then occlusion. Twenty-four hours later, the patches are uncovered and irradiated with a dose of UVR below the MED. After an additional 24 hours, the irradiated areas are examined; if there is a reaction only at the irradiated site, it is suggestive of a photosensitive reaction. The use of photopatch testing in clinical practice is largely limited to testing topical agents and compounds of sunscreens to diagnose photocontact dermatitis. Its use for the diagnosis of photoinduced cutaneous eruptions due to systemic medication has not been validated.[5]

Most photosensitivity drug reactions resolve with sun avoidance and drug discontinuation.[7] Patients who are unable to discontinue the offending agent will need topical steroids and protective measures are available to minimize symptoms, including broad-spectrum sunscreen and protective clothing. Currently, there is increasing concern about photosensitive premarketing studies, making photochemical reactivity screening an important part of drug development.[6]

Photosensitive drugs

Topical drugs

Miscellaneous topical drugs

Topical agents (Table 1) may cause two types of photo-related reactions: Photo-contact allergic dermatitis and topical phototoxicity.

Several topical drugs have been implicated in photocontact allergic dermatitis, such as acyclovir, dibucaine injection, hydrocortisone, chlorpromazine gel, and sunscreens.[8–11]

The majority of sunscreens that can produce a photoallergic reaction include p-aminobenzoic acid (PABA), benzophenones, cinnamates, salicylates, and octocrylene; however, newer sunscreens, such as Mexoryl SX, Tinosorb M, and Tinosorb S, are photostable molecules and are rarely associated with photosensitive reactions. Only one case of photoallergy has been reported due to Mexoryl SX.[12] Among sunscreens, oxybenzone is still the most commonly used UVR filter responsible for positive photopatch tests.[13]

Regarding topical phototoxicity, furocoumarins and coal tar have been implicated. Photoactive furocoumarins such as bergapten and 5- and 8-methoxypsoralen are compounds synthetized by plants and used in folk medicine, photochemotherapy, and in the cosmetic industry. A phototoxic reaction can also occur with inadvertent contact with these plants. When skin is exposed to furocoumarins and to ultraviolet light, a photosensitive reaction may occur, known as phytophotodermatitis. Plants rich in furocoumarins belong mainly to the families *Umbelliferae*, *Rutacea,* and *Moracea.* The most typical pattern of phytophotodermatitis is dermatosis bullosa striata pratensis, characterized by linear streaks beginning within 24 to 48 hours with prickling with erythema and, later, painful vesicles and bullae. It may continue as linear hyperpigmentation.[3,14]