

Evidence-Based Guidelines for the Classification and Management of Drug-Induced Phototoxicity

Introduction

Drug-induced phototoxicity, a non immunological event, refers to the development of rashes as a result of the combined effects of a chemical substance and ultraviolet radiation or visible radiation. Exposure to either the chemical or the light alone is not sufficient to induce the disease; however, when photoactivation of the chemical (chromophore; a radiation absorbing substance) occurs, the abnormal reaction may arise.

Most commonly, wavelengths within the UV-A spectrum (320-400 nm) cause drug-induced photosensitivity reactions, although occasionally some compounds have a peak absorption within the UV-B or visible range.

Incidence

The incidence of phototoxicity due to systemic medication varies greatly from drug to drug and even within subjects taking a particular agent. It usually relates to drug dosage, the local intensity of the relevant wavelengths and individual factors, such as skin type and drug handling. Phototoxic reactions develop in most individuals if they are exposed to sufficient amounts of light and drug. Typically, they appear as an exaggerated sunburn response. Photosensitivity reactions can occur also in darker skin types with heavily pigmented skin. Although the incidence of drug-induced photosensitivity is unknown, phototoxic reactions are probably more common than diagnosed or reported.

Mechanisms

Phototoxic reactions occur because of the damaging effects of photoactivated compounds on cellular structures such as cell membranes or DNA. Many compounds have the potential to cause phototoxicity. Most have at least one resonating double bond or an aromatic ring that can absorb radiant energy. In most instances, photoactivation of a compound results in the excitation of electrons from the stable singlet state to an excited triplet state. As excited-state electrons return to a more stable configuration, they transfer their energy to oxygen, leading to the formation of reactive oxygen intermediates. Reactive oxygen intermediates such as an oxygen singlet, superoxide anion, and hydrogen peroxide damage cell membranes and DNA. Signal transduction pathways that lead to the production of proinflammatory cytokines and arachidonic acid metabolites are also activated. The result is an inflammatory response that has the clinical appearance of an exaggerated sunburn reaction.

The exception to this mechanism of drug-induced phototoxicity is psoralen-induced phototoxicity. Psoralens intercalate within DNA, forming monofunctional adducts. Exposure to UV-A radiation leads to the formation of crosslinks within DNA. Exactly how these adducts cause photosensitivity is unclear.

Clinical features

1. The skin reaction occurs minutes to hours after exposure to agent and light

2. It appears most commonly as an exaggerated sunburn reaction. Rare forms with blisters and skin fragility may resemble porphyria cutanea tarda (pseudoporphyria) or can mimic chronic actinic dermatitis or lichen planus.
3. Vesicles, blisters and bullae may occur in severe reactions
4. It may or may not be itchy
5. Less commonly, skin may change colour, e.g. brown-greyish discoloration is associated with amiodarone medication
6. The reaction is limited to sun-exposed skin
7. Photo-onycholysis may arise with many oral photosensitising medications and may be the only sign of phototoxicity in dark-skinned individuals.
8. Susceptibility to photosensitivity can persist for several months after cessation of a photoactive drug.

Table 1. Major patterns of cutaneous phototoxicity

Skin reactions	Photosensitisers
Prickling or burning during exposure immediate erythema; oedema or urticaria with higher doses; sometimes delayed erythema or hyperpigmentation	Photofrin; amiodarone; chlorpromazine
Exaggerated sunburn	Fluoroquinolone antibiotics; chlorpromazine; amiodarone; thiazide diuretics; quinine; demethylchlortetracycline and other tetracyclines
Late onset erythema; blisters with slightly higher doses; hyperpigmentation only with low doses	Psoralens
Increased skin fragility with blisters from trauma (pseudoporphyria)	Nalidixic acid; frusemide; tetracycline; naproxen; amiodarone; fluoroquinolone antibiotics
Photoexposed site telangiectasia	Calcium channel antagonists

From: Ferguson J. Photosensitivity due to drugs. Photoderm Photoimmunol Photomed 2002, 18, 262-269.

Diagnostic Procedures

1. History taking and clinical examination. (Knowledge as to whether the eruption has been induced by light through thin clothing or window glass and how much light has been required often gives an indication of the responsible wavelength and severity.) Examination for photosensitive site involvement such as forehead, cheeks, chin, rim of ears, back of hands, with a clothing cut-off and the sparing of shadow sites such as beneath chin, behind ears and within the hair, as well as under spectacle frames and watch strap.
2. Drug history and an idea of the mechanism involved, will allow the correct diagnosis.
3. Phototesting with UV-A; UV-B; and, sometimes, visible light is helpful in diagnosing photosensitivity disorders. This test is performed as minimum erythema dose (MED) test by treating small areas of skin on the back or inner aspect of the forearms with

gradually increasing doses of light. Patients with phototoxic reactions have a reduced MED to UV-A or, in some instances to UV-B.

Laboratory Studies:

1. In doubtful cases to exclude porphyria cutanea tarda, urine porphyrin levels should be assessed.
2. Likewise if lupus erythematosus is suspected determine antinuclear antibody (ANA) and anti-Ro (SS-A) antibody levels.

Prevention and Treatment

The main goal of treatment is to identify the photosensitising agent and if possible to avoid it. In cases where medication is being taken to treat an existing condition and can not be discontinued, patients should be advised to follow sun protection strategies, including wearing sun protective clothing and using sunscreen if sunscreens are not the cause of the photosensitivity. Since most drug-induced photosensitivity reactions are caused by wavelengths within the UV-A range, sunscreens that strongly absorb UV-A should be prescribed.

Prognosis

In most patients, the prognosis is excellent once the offending agent is removed. However, depending on the elimination half-life of a drug complete resolution of the photosensitivity may take several weeks to months with some compounds.

Although mortality is rare, drug-induced photosensitivity can cause significant morbidity in some individuals, who must severely limit their exposure to natural or artificial light. The carcinogenic potential due to prolonged exposure to these photosensitizing drugs remains to be determined. For systemic psoralens as used in photochemotherapy (PUVA) the risk of squamous cell carcinoma is documented.

Patient Education

Patients need to be counselled regarding the possible photosensitizing properties of both prescription and non-prescription medications. Most often, appropriate sun protection measures prevent drug-induced photosensitivity reactions.

Patients with drug-induced photosensitivity reactions should be warned against the use of tanning beds and about potential cross-reactions of the offending drug. The risks of severe sunburn reactions, including the potential for and complications from widespread blistering reactions, should be discussed with the patient.

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Photosensitivity testing of new therapeutic molecules prior to marketing

A new molecule is required to have an absorption spectrum conducted. If it absorbs in the UVB/A or visible region, and is known to be distributed to skin or the eye, standard *in vitro* testing with a fibroblast 3T3 model follows. If phototoxicity is detected, human

volunteer testing may be recommended. (EMA, <http://www.emea.eu.int/pdfs/human/swp/039801en.pdf>) (FDA - <http://www.fda.gov/cder/guidance/3640fnl.pdf>).

The goal of photosafety testing is to detect the adverse effects of pharmaceutical products in the presence of light. This type of testing is relevant for medicinal products that enter the skin via dermal penetration or systemic circulation.

The overall risk benefit assessment of a drug product which induces adverse photoeffects will depend on considerations of the following factors:

1. The quality and potency of the effects detected in the preclinical and clinical studies.
2. The safety risks presented by the drug relative to its therapeutic potential.
3. The availability of clinically effective alternatives with a more favourable safety profile.

In most cases, data from *in vitro* tests may provide sufficient information for the preclinical assessment of the phototoxic potential of a drug product and thus *in vivo* nonclinical studies are normally not warranted. For a possible clinical follow-up testing on potential risks, controlled clinical studies e.g. determination of the minimal erythema dose (MED) in volunteers are encouraged. In case of potential risks identified either *in vitro* or in phototoxicity testing in human, an appropriate clinical safety survey should be performed both before and after marketing authorisation.

If a drug with clinically relevant findings in photosafety testing is granted a marketing authorization appropriate warning statements have to be included in the SPC/PIL. These should indicate that the drug may cause adverse photoeffects (effect to be specified) and users of the drug should avoid unprotected exposure to the sun while treated with the drug.

Many phototoxic drugs that have been marketed for years have never been studied in such detail. Usually they have post-marketing adverse reporting data but limited other information which historically was appropriate but now are out of date with standards that have improved considerably.

Table I. Drugs in current use reported to cause photosensitivity responses

Diuretic agents	Hydrochlorothiazide, furosemide (frusemide), chlorothiazide, bendroflumethiazide, benzthiazide, cyclothiazide, hydroflumethiazide, methyclothiazide, trichlormethiazide, polythiazide, ethacrynic acid, amiloride, triamterene, spironolactone, acetazolamide, metolazone, quinethazone.
Antimalarials	Chloroquine, quinine, mefloquine, pyrimethamine.
Antidepressants	Amitriptyline, trimipramine, nortriptyline, protriptyline, desipramine, amoxapine, imipramine, doxepin.
Cardiovascular drugs	Amiodarone, nifedipine, quinidine, captopril, enalapril, fosinopril, ramipril, disopyramide, hydralazine, clofibrate, simvastatin.
Nonsteroidal anti-inflammatory drugs	Naproxen, ketoprofen, suprofen, tiaprofenic acid, piroxicam, diflunisal diclofenac, mefenamic acid, nabumetone sulindac, phenylbutazone indomethacin, ibuprofen
Hypoglycaemics	Glibenclamide (glyburide), tolbutamide, glipizide tolazamide, chlorpropamide, acetohexamide

Antipsychotic drugs	Chlorpromazine trifluoperazine, prochlorperazine, thioridazine chlorprothixene, promethazine, haloperidol, thiothixene
Anticonvulsants	Carbamazepine, lamotrigine, phenobarbital (phenobarbitone), phenytoin, perphenazine, fluphenazine, promazine, triflupromazine, trimeprazine
Antihistamines	Cyproheptadine, diphenhydramine, brompheniramine, triprolidine, loratadine
Antimicrobials	Demeclocycline, nalidixic acid sulfamethoxazole, sulfasalazine ciprofloxacin, enoxacin, lomefloxacin, sulfamethizole, gentamicin, clofazimine, ofloxacin, norfloxacin oxytetracycline, tetracycline doxycycline, methacycline, minocycline trimethoprim, isoniazid griseofulvin, nitrofurantoin
Cytotoxic drugs	Fluorouracil, vinblastine dacarbazine, procarbazine, methotrexate
Hormones	Corticosteroids, estrogens, progesterones, spironolactone
Systemic dermatological agents	Isotretinoin, methoxsalen
Others	Gold salts, azathioprine, haematoporphyrin

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