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REVIEW ARTICLE

Drug-induced photosensitivity

Fotossensibilidade induzida por fármacos

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Abstract

Drug photosensitivity is a relatively frequent adverse event, although not always recognized due to its clinical polymorphism and difficulties in performing tests to prove drug causality.

The aim of this report is to review the mechanisms of photosensitivity related with topical and systemic drugs (phototoxicity, photoallergy, autoimmunity, and enhanced photocarcinogenesis), the main acute and delayed clinical manifestations (acute sunburn or eczema, pseudoporphyria, photo-onycholysis, dyschromia, telangiectasia, subacute lupus erythematosus, pre-cancerous lesions, and cutaneous neoplasia), the main culprits [non-steroidal anti-inflammatory drugs (NSAIDs), antimicrobials, like fluoroquinolones and tetracyclines, psychotropic, anticancer, and cardiovascular drugs] and the most adequate diagnostic procedures (photopatch and drug photoprovocation tests).

Keywords: Adverse drug event. Photosensitivity. Photoallergy. Phototoxicity. Photocarcinogenesis.

Resumo

A fotossensibilidade iatrogénica é uma reação adversa relativamente frequente, embora nem sempre reconhecida devido ao seu polimorfismo clínico e às dificuldades em realizar testes para provar a causalidade dos fármacos.

Pretende-se rever os mecanismos da fotossensibilidade relacionados com a exposição a fármacos tópicos e sistémicos (fototoxicidade, fotoalergia, auto-imunidade e ativação da fotocarcinogénese), as principais manifestações clínicas agudas e tardias (queimadura solar aguda ou eczema, pseudoporfiria, fotoonicólise, discromia, telangiectasia, lúpus eritematoso subagudo, lesões pré-cancerosas e neoplasias cutâneas), os principais fármacos responsáveis [anti-inflamatórios não esteróides (AINEs), antimicrobianos, como fluoroquinolonas e tetraciclinas, psicotrópicos, anticancerígenos e drogas cardiovasculares] e os procedimentos de diagnóstico mais adequados (testes fotoepicutâneos e testes de fotoprovocação oral).

Palavras-chave: Reação adversa medicamentosa. Fotossensibilidade. Fotoalergia. Fototoxicidade. Fotocarcinogénse.

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Introduction and basic concepts of pathogenesis

Photosensitivity is an abnormal cutaneous reaction from light exposure that can be induced or enhanced by topical or systemic drugs, used for therapeutic or diagnostic purposes or in an occupational setting[1,2]. Drug-induced photosensitivity is a potentially reversible adverse event that occurs when individuals are exposed to a drug and ultraviolet (UV) light or, eventually, visible light, but who tolerate the same amount of light exposure in the absence of the culprit drug[1,3].

Drug photosensitivity is certainly underrecognized as it presents under a wide spectrum of clinical patterns with different timelines concerning the relation to drug and light exposure[3], and because new culprits are regularly identified[4,5].

Photosensitizing agents are chromophores that after absorbing the energy of photons, most commonly from solar radiation, become activated and induce chemical reactions[6]. Drug photosensitivity is mostly related to UVA (320–400 nm), although some drugs produce reactions upon exposure to UVB radiation (290–320 nm) or even visible light (400–740 nm)[6]. Only few cases of exclusively UVB-induced drug photosensitivity have been documented[4,7].

Acute drug photosensitivity can result from non-specific inflammation–phototoxicity–or a specific immune reaction, mostly T-cell mediated–photoallergy–but other drug-induced or drug-enhanced immune reactions may occur, namely in drug-induced cutaneous lupus erythematosus (LE)[8].

Phototoxic reactions can also induce photoimmunosuppression and activate mechanisms involved in photocarcinogenesis and photoaging, responsible for late reactions (premature skin aging, lentigines, actinic keratosis, non-melanoma skin cancer [NMSC], and melanoma)[9,10].

Mechanisms of drug-induced photosensitivity

Phototoxicity

Following photoactivation of the drug present in the skin, the energy of UV photons excites the electrons in the outer orbits of the molecule and, as these electrons come to their ground energy state, the energy lost can produce photochemical modifications in the molecule (isomerization, breaking of double bounds, oxidation) or the energy can be transferred to neighboring molecules, initiating a chain of photochemical reactions. The energy can be directly transferred between two molecules (type I photochemical reaction) or the excited chromophore can react with oxygen, forming free radicals or reactive oxygen species (ROS) that will eventually also activate other molecules (type II photochemical reaction). If cell repair mechanisms (anti-oxidant responses, endonucleases for DNA repair) do not act immediately and control this chain reaction, neighboring molecules relevant for cell survival will be damaged, such as unsaturated lipids of cell membranes, aromatic amino acids of proteins/enzymes and pyrimidine bases of DNA or RNA. Cutaneous cells, namely keratinocytes, will therefore undergo apoptosis (sunburn cells) or necrosis as a result of these phototoxic reactions.

ROS or other abnormal molecules produced in this process will be recognized by intracellular sensors and induce the activation of intracellular signaling pathways (nuclear factor kappa B, mitogen-activated protein kinases, the Nrf-2 antioxidant response element pathway) and inflammasome, generating the secretion of prostaglandins, leukotrienes, interleukins (IL)—1, 6, 8, tumor necrosis factor-alpha (TNF-α), other cytokines and chemokines from keratinocytes and other cutaneous cells. Recruited inflammatory cells cause skin inflammation which becomes clinically apparent within 24–48 h. This is the classical phototoxic reaction that presents mostly as exaggerated sunburn with painful erythema, bullae or epidermal necrosis and on histology with sunburn cells and dermo-epidermal inflammation[1,2].

Photoallergy

In photoallergy, the energy of the UV photon transforms the chromophore into a stable photoproduct (photohapten) or enhances its bonding with an endogenous peptide, forming a photoallergen. By analogy with allergic and photoallergic contact dermatitis, it is suggested that skin antigen-presenting cells become activated and present the new hapten to T cells through human leukocyte antigen (HLA) molecules and costimulatory signals. Sensitized T cells, including memory and effector T cells, mostly Th1 and CD8+ cells, will be activated in a further encounter with the same or a similar chemical and generate a specific T-cell immune reaction, a type IV hypersensitivity reaction[11,12]. This adaptive T-cell specific immune reaction is mandatory for drug photoallergy, but as in phototoxicity, an initial photochemical reaction may be generated and an innate immune response may create “danger signals” that enhance T-cell sensitization through dendritic cell activation or the expression of adhesion molecules and

release of chemokine/cytokine by endothelial cells, fibroblasts, and keratinocytes. Together they promote antigen presentation and the migration of specific effector T cells into the dermis and epidermis, causing the allergic reaction. Therefore, as in allergic contact dermatitis (ACD) where the innate immune skin response to the allergen is well recognized as an important step towards sensitization[13], this also probably occurs in drug photoallergy.

Phototoxicity vs. Photoallergy

Drug photosensitivity is mainly due to phototoxicity, but some phototoxic chemicals can also induce photoallergic reactions in susceptible individuals[14]. Phototoxicity and photoallergy are not mutually exclusive and there are some overlapping aspects on pathophysiology and clinical presentations[15].

Classically, phototoxicity is more frequent, develops in every individual, as long as a sufficient concentration of the photosensitizer is present in the skin and concomitant exposure to UV in a dose-dependent way. Phototoxicity is somehow predictable, although individual susceptibility certainly exists, may occur after the first contact, and is not associated with flare-ups or cross-reactions in further exposures.

On the other hand, photoallergy develops only in a limited number of individuals, needs previous sensitization but can develop also with chemically similar substances (cross-reactions). It is not strictly dose-dependent and can occur even with low UV doses. Photoallergy presents mostly as pruritic eczema that can spread to non-exposed sites and takes *longer* to resolve, may become persistent and eventually progress to chronic actinic dermatitis with extreme photosensitivity with no further exposure to the culprit chemical. On histology, there is mainly a dermo-epidermal T-cell infiltrate with epidermal spongiosis and vesicles or a more lichenoid infiltrate. The reaction can usually be reproduced by a photopatch test, particularly in photoallergic contact dermatitis (Table 1)[16,17].

These two typical polar presentations of drug photosensitivity are easily recognized, but it is not always possible to distinguish between them based on the clinical aspects, histopathology, suspected culprit or results of photopatch or photoprovocation tests.

Except for a few chemicals with no intrinsic phototoxic potential that give rise to stable photoproducts and induce only photoallergy, like piroxicam[18], most substances can induce both phototoxic and photoallergic reactions.

Table 1. Main differences between phototoxicity from photoallergy

	Phototoxicity	Photoallergy
Frequency	High	Low
Latency period/ sensitization	No	Yes
Doses of UV/ photosensitizer	High	Low
Cross-reactions	No	Yes
Morphology of lesions	Sunburn, polymorphic	Eczema, erythema *multiforme*
Sharp limits	Yes	No
Covered areas	Not involved	Possibly involved
Resolution	Quick*	May recur, persistent reactors
Residual hyperpigmentation	Yes	No
Histology	Sunburn cells	Eczema
Pathomechanism	DNA/cell damage	Type IV hypersensitivity
	ROS/ inflammation	Photoproduct

*This relates only to the acute phototoxic reaction, but late effects as photoaging and photodarcinogenesis may also occur.

Other mechanisms of drug-induced/enhanced photosentitivity

Other immune pathomechanisms may also occur, as some drugs may enhance UV-induced expression of the Ro/SSA antigen on the surface of keratinocytes, interfere with apoptosis or cytokine production and promote photosensitivity and skin lesions in drug-induced subacute cutaneous LE[19].

Apart from acute phototoxicity, several phototoxic substances, like psoralens, chlorpromazine fluoroquinolones, and ketoprofen, also enhance chromosomal damage in the presence of UV light, both *in vitro* and *in vivo*[20-22]. These drugs can, therefore, behave as photogenotoxic and photomutagenic. Moreover, DNA aggressions also may cause photo-immunosuppression that further enhances photocarcinogenesis due to the lack of immunosurveillance against cancer cells[23]. These mechanisms related with fluoroquinolones have recently been reviewed[24].

Clinical presentations of drug photosensitivity

Systemic drug photosensitivity presents mainly as exaggerated sunburn or acute eczema on sun-exposed areas, but also as urticaria, lichenoid reactions,

telangiectasia, subacute cutaneous LE, bullae, hyperpigmentation, vitiligo-like lesions or NMSC (Table 2)[1].

Skin reactions may occur immediately after sun exposure in photosensitivity from vemurafenib, may occur within 1 or 2 days in most phototoxic or photoallergic contact dermatitis or systemic photoallergy, or within several days or weeks in pseudoporphyria, photo-onycholysis or subacute cutaneous LE, or even years, in skin aging and skin cancers enhanced by exposure to photoactive drugs.

In systemic drug photosensitivity the reaction usually involves the face and forehead, the V shaped area of the neck and upper chest, dorsum of the hands and forearms in a symmetric distribution. Shaded areas of the face (upper eyelids, upper lip, deep wrinkles) are usually spared (Fig. 1) as well as the retroauricular and submandibular areas and other facial areas covered by the beard or hair. Also, large body folds (axillae, groins, finger webs) and areas covered by clothing or accessories (watch strip, shoes) are also usually spared.

A different distribution of skin lesions can occur when sun exposure is asymmetric, as in car drivers who only expose the left arm/forearm. Occasionally, the lower lip is mainly or almost exclusively involved (Fig. 2), because of higher UV exposure and a thinner corneal layer[25,26], or the nails may be involved exclusively, as in photo-onycholysis (Fig. 3)[27].

In photoallergic or phototoxic contact dermatitis from topical drugs, lesions occur in the area of concomitant drug application and sun exposure, but distant lesions can occur in areas of accidental contact, as a in a contra-lateral limb (kissing faces of the legs) or in areas of inadvertent spread by the hands or contaminated objects[28,29]. Cases of connubial dermatitis have been described, mainly for ketoprofen and benzydamine[26,30-32]. When used as a mouthwash these non-steroidal anti-inflammatory drugs (NSAIDs) induce mostly lip and chin dermatitis[26,33].

Some topical drugs applied in large skin areas can be considerably absorbed and induce lesions in a distribution similar to systemic drug photosensitivity.

Immediate reactions

Immediate urticarial reactions, like photocontact urticaria, have been described with chlorpromazine[34] and with 5-aminolevulinic acid used in photodynamic therapy[35].

Amiodarone and benoxaprofen induce immediate prickling and burning with transient erythema[1]. Vemurafenib used as a single drug for metastatic melanoma induces immediate burning upon sun-exposure followed by well-limited painful edema and erythema that persist for a few days occurs in 22–66% of patients[8,36], but this reaction is less frequent when vemurafenib is associated with a MEK inhibitor[37]. A similar pattern has also been described with other BRAF inhibitors and other targeted therapies for cancer, namely the anaplastic lymphoma kinase (ALK) inhibitor brigatinib (Fig. 4)[38,39].

Table 2. Clinical patterns of photosensitivity, mostly involving phototoxicity or photoallergy or other immune-mediated reactions

Phototoxicity	Immune-mediated reactions
Exaggerated "sunburn"	Urticaria
Pseudoporphyria	Acute or subacute eczema
Photo-onycholysis	Erythema multiform-like
Hyperpigmentation	Lichenoid reactions
Hypopigmentation (vitiligo-like lesions)	Subacute/chronic lupus erythematosus
Telangiectasia	
Purpura	
Pellagra-like reactions	
Actinic keratosis and skin cancer	
Accelerated photoaging	

Acute photosensitivity

Non-pruritic and sometimes painful sharply limited erythema develops as an exaggerated sunburn in 12–24 h (Fig. 1), with vesicles and/or bullae in more severe forms. It progresses to desquamation and further to residual hyperpigmentation.

In acute drug photoallergy, lesions develop in 12–48 h in sensitized individuals and present mostly as confluent or non-confluent acute or subacute eczematous and pruriginous lesions that may affect also less exposed skin areas. After the culprit drug is stopped lesions usually resolve with no residual pigmentation, but they may progress to lichenification or persistent chronic photosensitivity, sometimes even after drug withdrawal.

In more severe cases of acute photoallergy, erythema-multiforme like lesions occur on photo-exposed and non-exposed areas, as in severe cases of photoallergic

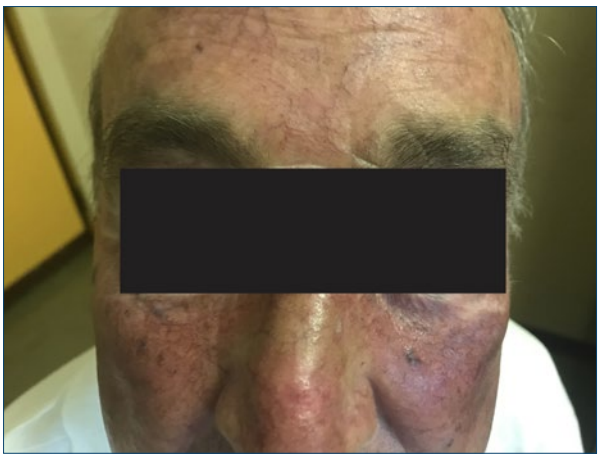

Figure 1. Acute phototoxicity from amiodarone that mimics sunburn and spares the deep facial wrinkles.

contact dermatitis from ketoprofen[40] or systemic drug photosensitivity from tocilizumab[41], vandetanib[42], or statins[43]. Photo-induced cases of Stevens–Johnson syndrome/toxic epidermal necrolysis have also been associated with drug photosensitivity[44].

Subacute patterns of drug photosensitivity

Drug induced pseudoporphyria develops within weeks to months and presents as chronic skin fragility with flaccid bullae on non-inflamed UV-exposed skin, occasionally progressing to milia. It resembles *porphyria cutanea tarda* both clinically and on histopathology (bullae below the *lamina densa* with scarce inflammation), but patients have no inborn error of porphyrin metabolism and no increase of endogenous porphyrins, although some drugs like voriconazole may transiently increase uroporphyrin levels[25].

Pseudoporphyria was initially described with nalidixic acid, furosemide, and naproxen, predominantly in children[1], but more recently, many other drugs have been associated with this phototoxic reaction: celecoxib[45], ciprofloxacin[46], voriconazole[47], torasemide[48], metformin[49], finasteride[50], and imatinib[51].

Photo-onycholysis is a typical pattern of phototoxicity, occurring often as the single manifestation. It presents as a half-moon distal onycholysis of one or several nails (Fig. 3). It appears 2–3 weeks after drug intake and sun exposure and is sometimes preceded by pain in the nail apparatus. It occurs mainly with tetracyclines (demethylchlortetracycline, minocycline, or doxycycline)[5], but has also been described with psoralens, fluoroquinolones[27], paclitaxel[52], and antipsychotic drugs[53].

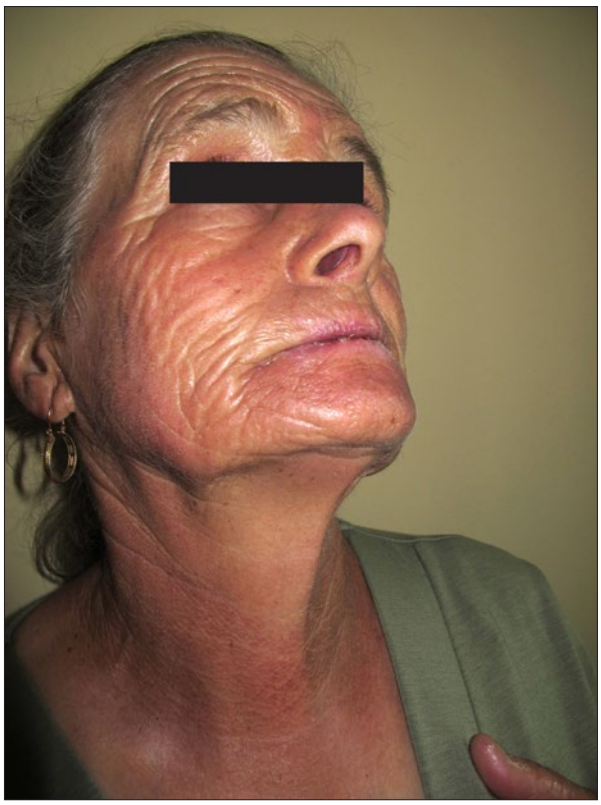

Figure 2. Photosensitivity from voriconazole with severe cheilitis and lip erosions.

There is no definite explanation for the exclusive nail involvement, but it may be related with less melanin in the nail bed and the nail plate may work as a lens to concentrate UV light[27,53].

Drug-induced cutaneous LE is probably underestimated. In a multicentre database analysis of the European Society of Cutaneous Lupus Erythematosus, drug induced cutaneous LE represented 6% among 1002 patients with cutaneous lesions and 13.2% of those with subacute cutaneous LE[54]. Drug-induced subacute cutaneous LE is usually associated with photosensitivity, mild systemic manifestations and, in >80% of the cases, with positive anti-Ro/SSA auto-antibodies, the hallmark of photosensitivity in LE.

Annular or papulosquamous lesions mimicking the idiopathic form of cutaneous subacute LE usually develop weeks or months after drug exposure (medium of 6 weeks) and can resolve on drug suspension[55]. Lesions are localized in photoexposed areas (face, neck, upper-chest, and arms), but also in usually UV-shaded areas[54]. Chronic cutaneous LE with more infiltrated plaques on the face or V of the neck can also be related with drugs.

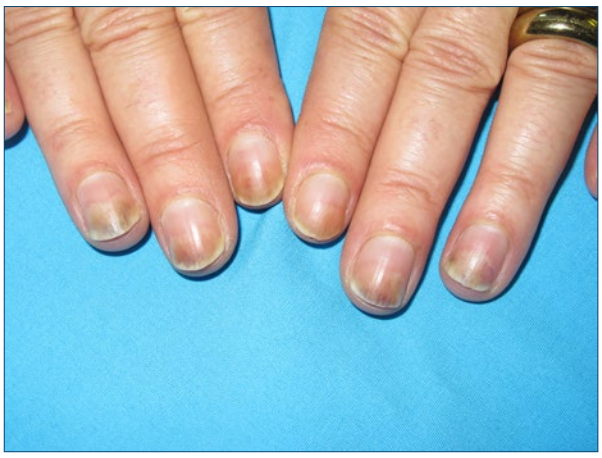

Figure 3. Photo-onycholysis from doxycycline.

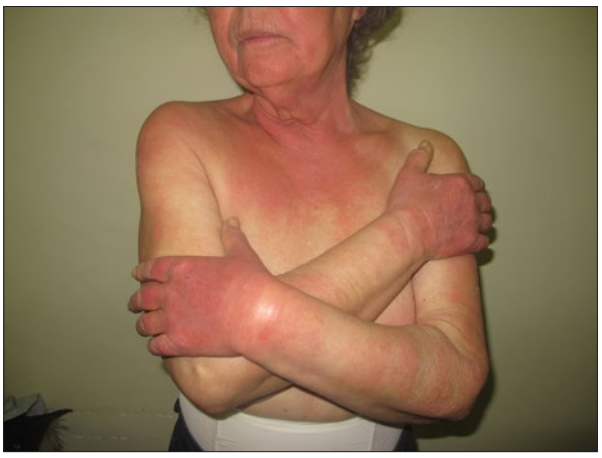

Figure 4. Acute phototoxicity from Brigatinib that shows as eczematous plaques involving the face, neck, forearms and hands, sparing non-sun-exposed areas.

Subacute cutaneous LE was described initially in association with thiazide diuretics, calcium channel blockers, ACE inhibitors[19], and more recently with terbinafine[8], the drug associated with the highest odds ratio for this adverse event[55]. Nowadays there is a long list of other drugs capable of inducing cutaneous LE[55], namely proton pump inhibitors[56], antiepileptics, TNF-α antagonists[55] and the anticancer taxanes, paclitaxel, and docetaxel[57].

Dyschromia corresponds to the residual hyper- or hypopigmentation which frequently follows acute phototoxicity. Similarly to the usual UV-induced pigmentary response, IL-1alfa stimulates keratinocytes to produce melanotropins that activate melanocytic pigmentation[58]. As for hypopigmentation (photoleukomelanoderma), it has been described in flutamide-induced photosensitivity (vitiliginous lesions with sharp limits after the acute reaction)[59], and hydrochlorothiazide[58].

Dyschromia with solar lentigines and other signs of photoaging have been recently described with voriconazole[60] and vandetanib[61].

Dyschromia from the accumulation of the photoactive drug or its metabolites in the dermis occurs in a smaller percentage of patients after acute phototoxicity from amiodarone, minocycline, or phenothiazines[62]. Some patients with lower phototypes also develop a golden-brown, slate gray, or bluish color on sun exposed areas, that persists *longer* after stopping amiodarone[1].

Other clinical patterns of subacute photosensitivity

Photo-distributed lichen *planus* or lichenoid reactions have been reported with several drugs, namely thiazides[63], tetracyclines[64], quinidine[65], capecitabine[66], and agents against hepatitis C virus (HCV)–simeprevir and sofosbuvir[67]. This may represent an individual reaction pattern of photosensitivity as it has been described with two different drugs in the same patient[68].

Telangiectasia as a manifestation of photosensitivity has been reported with nifedipine and other calcium channel blockers[1], venlafaxine[69] and with some cephalosporins[5,70]. A telangiectatic pattern of photoaging with lesions mainly in the lateral folds of the neck, sparing the shaded skin under the chin, is frequently observed in patients chronically exposed to the sun and photoactive drugs[70].

In rare cases, petechial purpura with sharp limits on the transition to the shaded areas was described with ciprofloxacin[71].

Pellagra is associated with the prolonged use of isoniazid, that consumes niacin for its metabolism, and pellagroid reactions were reported with the anticancer agents, like 6-mercaptopurine and 5-fluoruracil[5] and olanzapine[72].

Delayed and late effects of photosensitivity

Patients chronically exposed to photoactive drugs develop accelerated photoaging, actinic keratosis, and skin cancers, which, at least partially, can be explained by the photogenotoxic effect of some drugs. Voriconazole causing dyschromia, lentigines and actinic keratosis, even in children, is such an example[73].

Apart from psoralens, responsible for a dose-dependent increased risk of skin cancers after PUVA therapy[74], drugs like naproxen, chlorpromazine, and the

fluoroquinolones, particularly lomefloxacin, augment DNA aggression induced *in vitro* by UV and increase epidermal neoplasia in animals[75]. In humans, potentially photosensitizing drugs like diuretics and cardiovascular drugs are also being associated with increasing cutaneous pre-cancerous lesions[76] and recent reports correlate human short term exposure (weeks/months) to voriconazole or vemurafenib and long exposure to diuretics and anti-hypertensive drugs with an increased risk of developing NMSC and even melanoma[5,36,77,78].

Main drugs causing photosensitivity

The catalog of topical and systemic drugs inducing photosensitivity is large and constantly increasing and is not restricted to particular pharmacologic families. Photosensitivity is reported mainly with NSAIDs, antimicrobials (tetracyclines, fluoroquinolones, sulphonamides), psychotropic, cardiovascular, and anticancer drugs (Table 3).

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs cause photosensitivity when used topically and also after systemic use. Arylpropionic derivatives (benoxaprofen, carprofen, naproxen, suprofen, tiaprofenic acid, ketoprofen, and ibuprofen) have been frequently associated with phototoxicity, with tiaprofenic acid at 5% pet inducing phototoxic reactions in more than half of photopatch tested patients[79]. Other NSAIDs from this group have been reported to cause photoallergy, occasionally (carprofen and naproxen) or frequently (ketoprofen). Oral naproxen has been associated with photo-distributed erythema multiforme or lichenoid like-lesions, suggesting photoallergy[80], but also with pseudoporphyria[81]. Ketoprofen is the main cause of photoallergic contact dermatitis, although it seldom causes systemic photosensitivity probably due to the low levels reached in the skin after systemic use[82].

Ketoprofen used in gel or patches to relieve musculoskeletal pain has caused severe photoallergic reactions[83], often with edema, bullae or erythema multiform-like lesions, extending well beyond the area of application[84]. Reactions may recur on sun exposure with no further drug application, as ketoprofen persists in the epidermis at least for 17 days after application[84] and in contaminated objects, namely in clothing after machine washing[28].

Photoallergy from piroxicam, frequent 20–30 years ago[85,86], occurs in individuals with previous contact allergy to thiomersal[87], more precisely to its most frequent sensitizing moiety, thiosalicylic acid[88]. Actually, upon UVA irradiation, piroxicam decomposes and gives rise to a photoproduct, which is structurally similar to thiosalicylic acid and responsible for photoallergy[88].

Photosensitivity from piroxicam usually occurs within 24–48 h after the first drug intake and presents as an acute eczema involving diffusely the whole face or as scattered erythematous papules and vesicles on the face and dorsum of the hands and dyshidrosis[86].

Topical diclofenac, used for the treatment of actinic keratosis, has caused allergic and photoallergic contact dermatitis[89], sometimes with cross-reactions to aceclofenac[90].

Antimicrobials

Oral tetracyclines, doxycycline, and particularly demeclocycline are highly phototoxic and can induce exaggerated sunburn, photo-onycholysis, and pseudoporphyria[62]. Minocycline, though less phototoxic, can also induce a bluish persistent pigmentation and has caused photo-onycholysis (Fig. 3), like lymecycline[91].

Nalidixic acid has caused phototoxicity presenting often as pseudoporphyria[92] and the fluoroquinolones with a halogen at C-8 (fleroxacin, lomefloxacin, sparfloxacin, pefloxacin) also induce frequent phototoxic reactions (4–15% of treated patients), whereas this adverse reaction is less frequent with ciprofloxacin, norfloxacin, ofloxacin, and enoxacin[91]. Hyperpigmentation can occur after lomefloxacine[93] and ciprofloxacin have caused pseudoporphyria[46], purpura on photoexposed areas[71] and photo-induced Stevens–Johnson syndrome[44].

Sulfonamides, sulfa-drug analogs (thiazide diuretics, hypoglycemic sulfonylureas, and celecoxib), and dapsone (diaminodiphenylsulfone) have caused photosensitivity within the spectrum of UVB and UVA[5,62]. This adverse effect is not so frequent with cotrimoxazole, but trimethoprim has also been implicated[94].

On rare occasions, other antibiotics have been considered the culprits in photosensitivity, namely the antituberculous drugs isoniazid and pyrazinamide[5], and β-lactams ceftazidime and cefotaxime, the latter responsible for telangiectasia on sun-exposed areas[70].

The antifungal griseofulvin can cause an exaggerated sunburn-like reaction and aggravate LE[95], and terbinafine can also induce subacute LE in patients with anti-Ro antibodies and Rowell syndrome with photo-distribution of skin lesions[8].

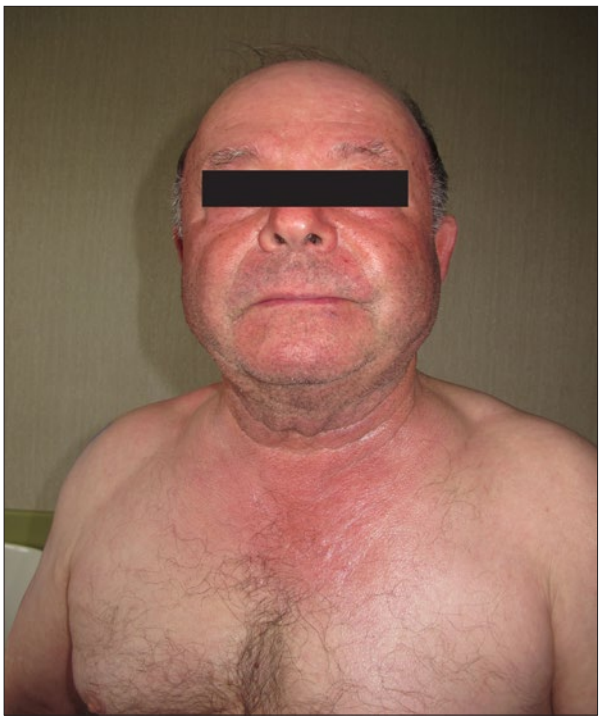

Figure 5. Photosensitivity from fenofibrate.

Among triazole antifungals, itraconazole has seldom been associated with photosensitivity[5], but phototoxicity affects more than 40% of patients treated with voriconazole *longer* than 4–6 months, particularly children[73]. Cutaneous reactions are dependent on broad UVA, extend to the visible solar spectrum[96], and include burning sensation immediately after sun exposure, sunburn like reaction, cheilitis, erosions of the lower lip (Fig. 3), and pseudoporphyria[47]. On relative short exposures (1–2 years), patients develop accelerated photoaging with solar lentigines and actinic keratosis that soon progress to multifocal invasive squamous cell carcinoma[9] or melanoma[10]. The immunosuppressed state of most patients on long-term voriconazole may enhance cutaneous carcinogenesis, but skin cancers related with voriconazole are distinct and more aggressive than those described in organ-transplanted or other immunosuppressed patients[97].

Antivirals used for human immunodeficiency virus (HIV) or HCV infection have been associated with photosensitivity confirmed by photopatch or photoprovocation tests[5]. Efavirenz induced mostly photo-distributed papulosquamous annular lesions within a few days or weeks of treatment[98] tenofovir induced a severe photo-distributed reaction with further generalization interpreted as a photoallergy[99] and the combination of faldaprevir and deleobuvir caused photosensitivity in more than a quarter of patients involved in controlled clinical trials[100].

The old antimalarials quinine and quinidine have frequently caused photoallergic and phototoxic reactions[101]. Chloroquine and hydroxychloroquine, mostly used in dermatology to prevent photosensitivity in cutaneous LE and polymorphic light eruption, paradoxically also cause photosensitivity[102] and a similar reaction has also been described with the combination of atovaquone and proguanil used in malaria prophylaxis[103].

Psychotropic drugs

Phenothiazines used systemically as antipsychotics (chlorpromazine, thioridazine, and flupenthixol) are typically phototoxic and cause sunburn, bullous and lichenoid eruptions, and photo-distributed slate-gray hyperpigmentation on the long term[5]. Olanzapine has caused several cases of photosensitivity[53,72], as well clozapine, haloperidol, and riperidone[5].

Photoallergy occurs frequently after contact with phenothiazines, namely with creams containing promethazine or isothipendyl chlorhydrate used as topical antipruritics[85] chlorproethazine cream used for muscle pain[104] or chlorpromazine manipulated by caregivers[105].

Among antidepressants, tricyclic drugs imipramine and clomipramine, as well as the newer selective serotonin reuptake inhibitors, fluoxetine, paroxetine, fluvoxamine, venlafaxine, and sertraline, have been proven as occasional causes of photosensitivity, similar to the anxiolytics alprazolam and chlordiazepoxide[5].

Cardiovascular drugs

Soon after its introduction in the market, the diuretic hydrochlorothiazide was recognized as a cause of photosensitivity, often proven by positive photopatch tests. Exaggerated sunburn, photo-distributed eczema, lichenoid reactions, dyschromia, persistent photosensitivity[106] and more recently increase of actinic keratosis and NMSC have been related with its wide use[76].

The antiarrhythmic amiodarone frequently causes phototoxicity (7–50% of patients) presenting as burning/tingling sensation on sun-exposure, followed by erythema, eczema and a bluish-gray hyperpigmentation in sun-exposed areas due to the dermal accumulation of drug metabolites[107].

Other cardiovascular drugs have been associated with photo-induced reactions, like amlodipine and nifedipine (telangiectasia)[108,109], diltiazem (lichenoid reaction with

Table 3. Main drugs causing photosensitivity

1. Nonsteroidal anti-inflammatory drugs (NSAIDs)
Arylpropionic acids:
Ketoprofen[*,‡], tiaprofenic acid[†], suprofen
Naproxen[¶], ibuprofen, ibuproxam, carprofen[‡]
Piroxicam[*,‡], etofenamate[*,‡]
Benzydamine[‡]
Celecoxib[¶], diclofenac[‡]
2. Antimicrobials (antibiotics, antifungals, antivirals, antimalarials)
Tetracyclines[†] (doxycycline, minocycline, limecycline)
Fluoroquinolones[**] (lomefloxacin[†], ciprofloxacin[*])
Sulphonamides (sulfamethoxazole, dapsone)
Isoniazid/pyrazinamide
Voriconazole[†,**], itraconazole, terbinafine
Efavirenz, tenofovir, faldaprevir
Quinine, chloroquine, hydroxychloroquine
3. Psychotropic and related drugs
Phenotiazines (chlorpromazine[‡], thioridazine)
Promethazine[*,‡], chlorproethazine[*,‡]
Imipramine, clomipramine
Serotonin reuptake inhibitors
4. Cardiovascular drugs
Amiodarone[†], quinidine
Hydrochlorothiazide[*,**], furosemide, torsemide
Calcium-channel blockers (amlodipine, nifedipine)
5. Anticancer drugs
Classical chemotherapy
Methotrexate, 6-mercaptopurine, azathioprine, 5-FU
Placlitaxel and taxanes
Dacarbazine, vinblastine
Targeted therapies
Vemurafenib[**]
Imatinib[¶], sunitinib[¶]
Erlotinib, vandetanib, pazopanib
Brigatinib
6. Miscellaneous drugs
Psoralens[**]
Fenofibrate[*], simvastatin, atorvastatin
Sulfonylureas, sitagliptin, metformin
Flutamide, finasteride
Pirfenidone
Porphyrin analogs for photodynamic therapy
Retinoids (isotretinoin)
7. Plants (used as drugs) [†]
Hypericum perforatum (St John's wort)
Ruta graveolans (common rue)[‡]
Kava extracts

[*]Mainly photoallergic.
[†]Mainly phototoxic.
[‡]Often also from topical exposure or airborne exposure, mainly in occupational settings.
[¶]Often associated with *porphyria cutanea tarda*.
[**]An increase of actinic keratosis, NMSC and, occasionally, melanoma have been related with these drugs.

hyperpigmentation)[110], furosemide/torsemide (pseudoporphyria, subacute LE, photo-onycholysis) and, very occasionally, angiotensin conversing enzyme inhibitors (lisinopril, enalapril, and ramipril), candesartan and the β-blockers atenolol and bisoprolol[4].

Anticancer drugs

Many classical anticancer drugs and particularly new targeted therapies have been increasingly associated with photo-induced cutaneous lesions[38]. Examples of classical drugs include the antimetabolites, methotrexate (sunburn recall reaction), 5-fluoruracil and related capecitabine and tegafur (sunburn, lichenoid and eczematous reactions, hyperpigmentation), 6-mercapto-purine and azathioprine (pellagra-like reactions and photocarcinogenesis)[4], dacarbazine[5], paclitaxel and other taxanes (erythema multiforme, photo-onycholysis, drug-induced LE)[111] and vinblastine[5].

Among new targeted therapies, photosensitivity has been described with imatinib (several cases of pseudoporphyria)[51], sunitinib (pseudoporphyria)[112], brigatinib (sunburn like reaction)[39], erlotinib[113] (also with acne-like reactions predominating in sun-exposed areas), crisotinib[5], pazopanib (phototoxicity and hyperpigmentation)[114], vandetanib (phototoxic and several photoallergic reactions with erythema multiforme-like aspects, confirmed by photopatch tests)[61,114], and, particularly, with vemurafenib. When used as a single therapy in metastatic melanoma up to two thirds of patients develop vemurafenib photosensitivity in the spectrum of UVA presenting as immediate burning and painful sensation and a sharply demarcated erythema and edema that appear still during UV irradiation, resembling solar urticaria, but erythema and edema persist for a few days[77].

Other drugs

Despite its recognized phototoxic potential, the anti-fibrotic agent pirfenidone was released for the treatment of interstitial lung disease and has caused phototoxic reactions with photoleukomelanoderma[115] and photoallergy with lichenoid reactions and positive photopatch or photoprovocation tests[11 6].

Fenofibrate can cause photoallergy with lichenoid and eczematous reactions (Fig. 5) due to its benzophenone structure and often exhibits cross-reactions with ketoprofen[117]. Statins, both simvastatin and atorvastatin, have also induced photosensitivity with reduced sensitivity to UVA[4].

Retinoids, namely isotretinoin increases UV sensitivity, and very occasionally photosensitivity has been described with antidiabetics (glibenclamide and sitagliptin), the anticonvulsant carbamazepine[4], flutamide[118], and finasteride[50] and even with amoxicillin[119]. Therefore, all suspected drugs have to be considered and photopatch or photoprovocation tests should be performed to establish a correct diagnosis.

Moreover, photosensitivity can be due to “folk” medicines, mostly based on plant extracts rich in furocoumarins, like “home-made” infusions of St. John’s wort (*Hypericum perforatum* L.) used to treat depression[120] or *Ruta graveolans* infusions applied topically to relieve pain in fibromyalgia[121].

Diagnostic Procedures in Drug Photosensitivity

In suspected drug photosensitivity, it is very important to question the onset of drug use and the relation with sun exposure, with a particular emphasis into the amount and type of sun light received, including through a window glass which allows permeation of UVA mostly involved in drug photosensitivity. In typical cases of photosensitivity after exposure to a known photosensitizer and resolution on drug withdrawal, no additional tests are required.

Photopatch tests are indicated mainly for confirming the etiology of photoallergic contact dermatitis, but they can also be useful in the study of systemic drug photosensitivity[122]. For this procedure, allergens in patch test chambers are applied in duplicate on the back, followed by skin irradiation of one of the sets of allergens at day 1 or day 2 with 5 J/cm^2 of UVA, whereas the other set is shielded from light. Readings should be performed immediately after irradiation and also 48 and/or 72 h thereafter, comparing the irradiated vs. non-irradiated area of the back. Positive reactions both in the irradiated and non-irradiated sites mean contact allergy, that may be photoaggravated if the reaction is 1+ more in the irradiated site. A photopatch test is positive when erythema and papules covering the whole test area are observed only in the irradiated side[123,124]. If the reaction is mainly erythema and edema, without pruritus, exclusively limited to the test chamber area, with very sharp limits, begins shortly after irradiation, reaches its highest intensity by 24 h and regresses by 48/72 h (decrescendo reaction) with hyperpigmentation, it suggests a phototoxic reaction. A pruritic erythema with vesicles, diffuse limits extending beyond the

chamber limit, increasing in intensity until 48/72 h after irradiation (crescendo reaction), suggests photoallergy[125]. Often these patterns are not so typical and the difficulties previously referred in the interpretation of clinical cases also occur in the interpretation of the photopatch tests.

The recommended European baseline photopatch test series includes many topical and systemic drugs, namely ketoprofen, etofenamate, piroxicam, benzydamine, and also piketoprofen, dexketoprofen, ibuprofen, diclofenac, fenofibrate, and chlorpromazine in the extended series[89]. In the absence of standardized commercial allergens, which are really few for the study of systemic drug photosensitivity, drugs can be photopatch tested after the powder of the commercial drug is incorporated in petrolatum or in water, as recommended for the study of other non-immediate cutaneous drug eruptions. Photopatch tests are often positive in photoallergy to piroxicam[86], ketoprofen[126], fenofibrate[117], and also occasionally with hydrochlorothiazide[106], lomefloxacin[15], pirfenidone[116], and vandetanib[61].

Photoprovocation is also helpful to confirm the culprit in systemic drug photosensitivity[4]. For photoprovocation small areas of the back/buttocks are irradiated with increasing UV doses and, if possible, different UV-wavelengths. Readings are performed immediately or within 24/72 h. Reaction to very low UV doses for the phototype or a significant difference in the minimal erythema dose (after UVA or UVB irradiation) between phototests performed while the patient is exposed to the drug or after its withdrawal is considered positive.

Photoprovocation using a monochromator allows identification of the precise UV-wavelength responsible for the photosensitivity in order to avoid it in future drug exposures.

With highly phototoxic drugs, both photopatch and photoprovocation tests can be positive in the majority of tested individuals, therefore, they are not particularly useful for confirming the etiology of a phototoxic reaction, but they can disclose a hidden photoallergy.

Conclusions

Phototoxic, photoallergic, and overlapping photosensitive reactions are still a frequent problem. They have highly polymorphic clinical presentations with different time courses concerning exposure to the drug and to the sun, and therefore the diagnosis can be difficult. Main culprits depend on geographic areas and over time, mostly related to prescription habits. The dermatologist must be highly alert to search for a possible involvement of a drug in a photosensitive patient and try to confirm its contribution to photosensitivity. A correct questionnaire should be conducted, and although not so important in phototoxic cases, complementary tests including photopatch and photoprovocation tests may contribute to the final etiologic diagnosis. This is important in order to allow an adequate patient advice concerning further eviction of the photosensitizer and related chemicals, which, apart from acute symptoms, are being increasingly associated with accelerated photoaging and enhancement of skin cancers.

What does this study add?

Clinical manifestations of drug phototosensitivity are polymporphic and, apart from exaggerated sunburn and acute eczema, can also present as erythema multiforme, pseudoporphyria, photo-onycholysis, dyschromia, lichenoid reaction, telangiectasia or purpura on sun-exposed areas and subacute LE or enhance photoaging and risk of NMSC (or melanoma).

- Main topical drugs causing photosensitivity are the NSAIDs, particularly ketoprofen and systemic drugs also include NSAIDs, fluoroquinolones, tetracyclines, thiazides, and phenothiazines, but a few new drugs have been described as culprits.
- Photopatch testing, indicated mainly for the study of photoallergic contact dermatitis, can also be useful in systemic drug photosensitivity.

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