Drug Photosensitivity

23

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Key Points

- Clinical manifestations of drug photosensitivity are polymorphic.
- Acute exaggerated sunburn and eczema of photoexposed sites are the main presentations of systemic photosensitivity.
- Pseudoporphyria, photoonycholysis, dyschromia and subacute lupus erythematosus are forms of subacute drug photosensitivity.
- It is not always easy to distinguish phototoxicity from photoallergy and both mechanisms can be involved in the final reaction.
- Main topical drugs causing photosensitivity are the NSAIDs, particularly ketoprofen.
- Photopatch testing, indicated mainly for the study of photoallergic contact dermatitis, can also be useful in systemic drug photosensitivity.

Definition and Epidemiology

Drug photosensitivity is an abnormal skin reaction to light, usually ultraviolet (UV) light, in individuals exposed to a drug, who, tolerate the same amount of light exposure in the abscence of the culprit drug.

Drug photosensitivity can present under a wide spectrum of acute or delayed clinical patterns, which are important to recognize and distinguish from idiopathic photodermatoses, in order to remove the offending drug or take the adequate measures to reduce this adverse effect.

Some drug phototoxic reactions presenting as acute sunburn or acute photoallergic eczema on sun-exposed areas are well recognized, but other reactions are often misdiagnosed, as the relation between drug and sun exposure may not be so obvious. The involvement of drug is certainly underestimated in drug-induced lupus erythematosus (LE) or in actinic keratosis and nonmelanoma skin cancer (NMSC) in patients exposed to photoactive drugs (Placzek et al. 1999).

More than 300 drugs from different pharmacological groups can cause photosensitivity, namely systemic or topical drugs and, occasionally, drugs manipulated in an occupational setting.

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A.D. Katsambas et al. (eds.), *European Handbook of Dermatological Treatments*,
DOI 10.1007/978-3-662-45139-7_23,

Many photosensitizers have been recognized and removed from the market (benoxaprofen, chlorproéthazine); premarketing studies regularly performed prevent the release of potential photosensitizing drugs; and when photosensitizers are used (lomefloxacin, vemurafenib), sun avoidance/protection is recommended (Gelot et al. 2013). Nevertheless, with the constant development of new photosensitizers, namely, for therapeutic purposes (photodynamic therapy), the introduction of new drugs with distinct mechanisms of action, namely, new targeted therapies, and more severe patients with concomitant diseases (immunosuppression), it is difficult to avoid this adverse drug effect.

Photosensitivity is still a field of intense research, with new mechanisms of drug photosensitivity and new aspects of their clinical presentation being recognized, which may also be important to understand diseases that course with photosensitivity, like HIV infection. Moreover, different pathomechanisms underlying drug photosensitivity may explain their clinical expressions and orient the choice of the most adequate diagnostic tests and therapeutic and preventive measures.

Basic Concept of Pathogenesis

Classically, drug photosensitivity is divided into phototoxicity (the more frequent) and photoallergy, but there are many overlapping situations and other immune-mediated or nonimmune-mediated mechanisms can also be involved. Most reactions occur within the UVA wavelength, although some can extend to visible light or, also, to UVB.

Immune-mediated reactions are mostly T-cell-dependent reactions, responsible for photoallergic contact dermatitis and systemic photoallergy. Drug-induced or drug-enhanced autoimmunity with photosensitivity involves autoantibodies and an inflammatory response with involvement of T cells.

Drug phototoxicity, on the other hand, does not involve specific immune hypersensitivity reactions. Frequently, acute reactions can be associated with enhanced photoimmunosuppression, photocarcinogenesis and photoaging, responsible for late reactions (premature skin aging, lentigines, actinic keratosis, NMSC and, even, melanoma) (Gonçalo 2012).

Solar Light and UVR in Drug Photosensitivity

Artificial light can be involved in drug photosensitivity (UV lamps used for aesthetic or therapeutic purposes or UV sources in occupational settings), but natural sun exposure is usually the cause. From the solar spectrum that reaches the earth, UV radiation, particularly UVA (320–400 nm), is responsible for most cases of photosensitivity. Some chromophores absorb in the UVB (290–320 nm) and UVB is more energetic, but UVA penetrates the skin more deeply and, particularly for systemic drugs, this is certainly the most important part of the solar spectrum involved in drug photosensitivity. Only exceptional cases of exclusively UVB-induced drug photosensitivity have been documented (Fujimoto et al. 2009).

Mechanisms of Acute Drug Phototoxicity

Photosensitivity develops when an abnormal chromophore is present in the skin, when a normal chromophore is present in exaggerated amounts or when there is failure of normal defensive mechanisms. The drug or a drug metabolite may be the exogenous chromophore that is excited in the skin or the drug may increase the quantity of endogenous chromophores in the skin, and these are, finally, responsible for the inflammatory reaction.

When a chromophore in the skin receives the energy of a UV photon, the electrons in the outer orbits increase their energy, and the molecules enter a short-lived excited state, singlet state, or can undergo more long-lived modifications into biologically more active molecules, triplet state. Excited molecules react with

neighbouring molecules in a photodynamic reaction, involving oxygen (type I) or other molecules (type II), and, ultimately, induce changes in bioactive molecules (unsaturated lipids of cell membranes, aromatic amino acids of proteins and pyrimidine bases of DNA or RNA). Eventually, free radicals or reactive oxygen species (ROS) are formed and expand the reaction in a cascade of events that progress in the absence of effective repair mechanisms (antioxidative defence mechanisms). This will result in damage of cellular organelles (mitochondria, lysosomes and cell membranes), cell aggression or cytotoxicity (apoptosis) of keratinocytes, melanocytes, dendritic cells in the epidermis and, eventually, other cells in the dermis. Injured cells liberate inflammatory mediators (prostaglandins, leukotrienes, IL-1, IL-6, TNF-alfa, IL-8/CXCL8, other cytokines and chemokines), and inflammatory cells are recruited causing visible skin lesions.

Other Mechanisms of Drug Phototoxicity

In rare cases, the drug increases the concentration of endogenous photosensitizers. Elevated erythrocyte porphyrins, namely, zinc protoporphyrin, seem responsible for acute photosensitivity from vemurafenib. Actually, transient skin burning shortly after sun exposure followed by erythema and oedema clearly limited by protective clothing, lasting a few days, simulates the genetic erythropoietic porphyria. Other kinase inhibitors that interfere with porphyrin metabolism, namely, vandetanib and, less often, imatinib and sorafenib, also cause acute photosensitivity.

Protoporphyrins, elevated during treatment with docetaxel, may also be responsible for photosensitivity.

Other porphyrins, namely, uroporphyrins, were increased in a case of photosensitivity from voriconazole associated with porphyria cutanea tarda, although voriconazole induces mostly pseudoporphyria with normal porphyrin levels.

Increased endogenous retinoids were explored as a possible cause of voriconazole photosensitivity, but this was not proved, although exogenous retinoids increase photosensitivity from this antifungal.

A decrease in defensive mechanisms, with reduced vitamin PP (niacinamide), may also contribute to vemurafenib photosensitivity.

Drug Photoallergy

In photoallergy, the energy of the photon transforms the drug into a stable photoproduct or enhances its combination with an endogenous peptide, forming a hapten or an antigen. Dendritic cells will uptake this antigen and combine it with HLA molecules, and in an adequate environment in skin-draining lymph nodes (cytokines/chemokines and HLA and co-stimulatory molecules), they stimulate and, eventually, sensitize naïve T cells. As in allergic contact dermatitis, drug-specific T cells will be mostly responsible for the effector response.

Mechanisms to explain how drugs enhance cutaneous LE, particularly the subacute variant, are not completely understood. Drugs may enhance UV-induced expression of the Ro/SSA antigen on the surface of keratinocytes and may interfere with apoptosis or cytokine production, promoting photosensitivity and the development of skin lesions in susceptible individuals.

Drug-Induced/Drug-Enhanced Photocarcinogenesis

Apart from the capacity to generate free radicals and cell death responsible for acute phototoxicity, several phototoxic substances, like psoralens, chlorpromazine, fluoroquinolones and ketoprofen, also enhance chromosomal damage in the presence of UVR, as shown both in *in vitro* and *in vivo* studies (Ray et al. 2013). These drugs are, therefore, photogenotoxic, photomutagenic and, consequently, photocarcinogenic. Moreover, this type of DNA aggression is also usually associated with photoimmunosuppression which further enhances photocarcinogenesis.

Epidemiological studies, reported since 1999, called the attention to the association between actinic keratosis and the exposure to potentially photosensitizing drugs (Placzek et al.1999), and

recent reports reinforce this association, namely, for diuretics and cardiovascular drugs, even if patients do not develop acute signs of photosensitivity (Jensen et al. 2008; Traianou et al. 2012). Nonmelanoma skin cancer (NMSC) and melanoma are also increased in humans chronically exposed to photoactive drugs, namely, psoralens, voriconazole and vemurafenib (Miller et al. 2010; Rinderknecht et al. 2013; Stern et al. 2012).

DNA damage in the presence of UVR and drugs may not be the only mechanism of voriconazole- or vemurafenib-enhanced photocarcinogenesis. Activation of alternative oncogenic intracellular pathways due to BRAF inhibition in vemurafenib and previous immunosuppression in voriconazole-treated patients may also contribute to enhancing carcinogenesis.

Drug Photosensitivity: Phototoxicity Versus Photoallergy

Although mechanisms involving T-cell-mediated photoallergy and nonspecific acute phototoxicity are well individualized, their participation in each case of drug photosensitivity is often more complex. Except for a few drugs, as piroxicam, which do not have an intrinsic phototoxic potential and induce only photoallergy, most substances can induce both photoallergic and phototoxic reactions.

In theory, in the clinical setting, it is easy to differentiate photoallergy from phototoxicity, but there are many overlapping aspects.

Classically, photoallergy develops only in a limited number in individuals and needs previous sensitization but occurs also with cross-reactive chemicals. It is not dose dependent, develops on low UV dose and appears as eczema that can spread to non-exposed sites, and on skin biopsy, there are mainly T-cell infiltration, spongiosis and vesicles. Phototoxicity is more frequent, develops in every individual and, as long as enough photosensitizer and sun exposure are simultaneously present, it occurs on a first contact with no particular aggravation on further contacts. It is not associated with cross-reactions, presents mainly as well-demarcated erythema, exclusively on sun-exposed areas (mimicking sunburn), resolves with hyperpigmentation and apoptotic keratinocytes (sunburn cells) are abundant on histology (Table 23.1).

These are the two polar aspects of photosensitivity, but many molecules may induce both phototoxic and photoallergic reactions, and, in the same patient, aspects that resemble phototoxicity may coexist with others that suggest photoallergy.

The highly phototoxic furocoumarins, contained in plant extracts ingested or used topically in "folk medicine" or during photochemotherapy, can induce photoallergy in some individuals

Table 23.1 Distinction between phototoxicity and 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[a]	May recur, persistent reactors
Residual hyperpigmentation	Yes	No
Histology	Sunburn cells	Eczema
Pathomechanism	DNA/cell damage	Type IV hypersensitivity
	ROS/inflammation	Photoproduct

[a]This relates only to the acute phototoxic reaction, but late effects as photoaging and photocarcinogenesis may also occur

(skin lesions developing at very low concentrations of psoralens and UV light). Also, phototoxic drugs like promethazine and lomefloxacin can induce photoallergy.

Very probably, photoallergens, as photoactive molecules, may also have some inherent phototoxic potential, like contact allergens that have some "irritant" capacity. In allergic contact dermatitis, most contact allergens induce "danger signals" that are recognized by innate receptors in skin cells and awaken the adaptive immune system, promoting sensitization. An innate inflammatory reaction generated in skin, in the presence of photoactive molecules and UVR, can also act as the "danger signal" necessary to initiate the sensitizing process.

Although phototoxicity can occur on a first contact and photoallergy needs previous sensitization, individuals previously sensitized to a structurally similar molecule can develop the reaction on a first exposure. This occurs in individuals with contact allergy to thiomersal and its moiety, thiosalicylic acid, who develop photoallergy to piroxicam on the first drug intake. Upon UVA irradiation, piroxicam is photodecomposed into a molecule antigenically and structurally similar to thiosalicylic acid that is responsible for the photoallergic reaction (Serra et al. 2008).

Also, patients with contact allergy to perfumes (cinnamic alcohol), octocrylene or benzophenones may have photoallergic contact dermatitis from ketoprofen on a first exposure or vice versa, as there are conformational similarities between these molecules.

Phototoxicity is considered to occur in every patient, as long as enough chromophore and sun are present at the same time, but even in drug phototoxicity, there are particularly susceptible individuals, even though mechanisms underlying this susceptibility have not been characterized.

Clinical Presentation

The clinical patterns of systemic drug photosensitivity vary from urticaria through eczema or subacute LE up to vitiligo-like lesions or NMSC. They can be very typical as in acute exaggerated sunburn, but sometimes, the diagnosis or even the suspicion of drug photosensitivity is not so obvious (Table 23.2).

Skin reactions can occur immediately after sun exposure in vemurafenib-induced photosensitivity, but skin lesions may be delayed 1 or 2 days in most phototoxic or photoallergic contact dermatitis or systemic photoallergy, several days or weeks in pseudoporphyria or subacute LE or even years in skin cancers associated with a long exposure to the sun and the photoactive drugs.

In systemic drug photosensitivity, the reaction usually involves, in a symmetric distribution, the face and forehead, the V-shaped area of the neck and upper chest, dorsum of the hands and forearms. Shaded areas in the face (upper eyelids, upper lip, deep wrinkles) are usually spared (Fig. 23.1) as well as retroauricular areas, submandibular areas (Fig. 23.2) and areas covered by the beard or scalp hair. In more extensive sun exposure, large body folds, like the axillae, groins, finger webs and areas covered by clothing or other accessories (watch strip, shoes) are also usually spared. Involvement of the shaded areas suggests an airborne dermatitis, which may occur in occupational exposure to photoactive drugs, in nurses and caregivers who crash tablets or during drug manufacture.

A different pattern in the distribution of skin lesions can occur when sun exposure is asymmetric, as in car drivers who only expose the left

Table 23.2 Clinical patterns of photosensitivity

Predominant in phototoxicity	Predominant in photoallergy
Exaggerated "sunburn"	Urticaria in sun-exposed area
Pseudoporphyria	Acute or subacute eczema
Photoonycholysis	Cheilitis
Hyperpigmentation	Erythema multiforme-like
Hypopigmentation (vitiligo-like lesions)	Lichenoid reactions
Telangiectasia	Subacute or chronic lupus erythematosus
Purpura	
Pellagra-like reactions	
Actinic keratosis and squamous cell carcinoma	

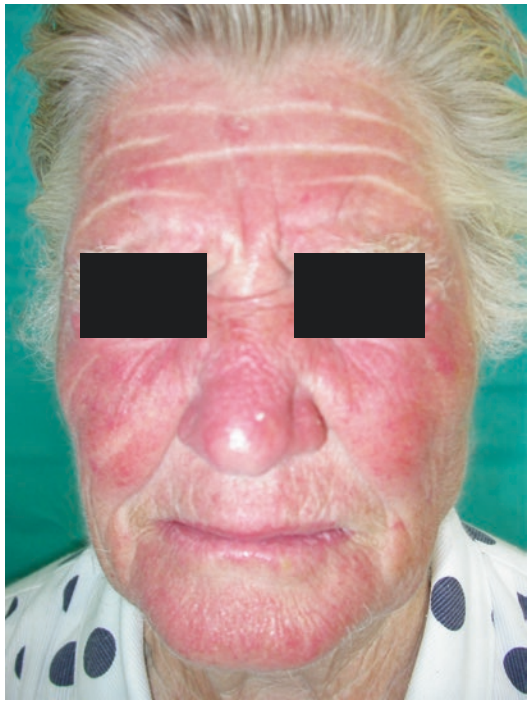

Fig. 23.1 Acute phototoxicity from amiodarone that mimics sunburn and spares the deep facial wrinkles

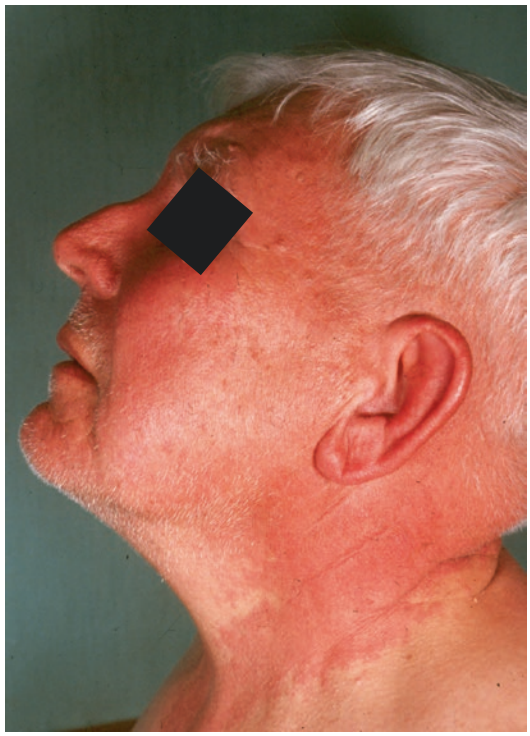

Fig. 23.2 Photosensitivity from systemic piroxicam, sparing the shaded submandibular area

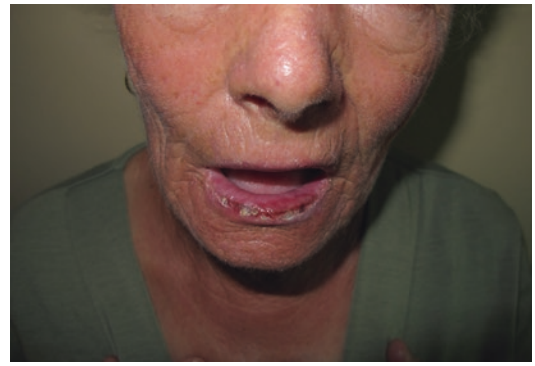

Fig. 23.3 Photosensitivity from voriconazole with severe cheilitis and lip erosions

arm. Sometimes, in systemic photosensitivity, the lower lip is mainly or almost exclusively involved (Fig. 23.3), because of its higher exposure and, very probably, because the corneal layer is thinner and, therefore, more prone to photosensitivity.

In photoallergic or phototoxic contact dermatitis from topical drugs, lesions are coincident with the area of drug application and concomitant sun exposure, but distant lesions can occur in areas of accidental contact, as in a contralateral limb (kissing faces of the legs), or in areas of inadvertent spread by the hands or contaminated objects. Cases of connubial dermatitis have been described, mainly for ketoprofen and benzydamine (Devleeschouwer et al. 2008. When used in the mouth these NSAIDs induce mostly lip and chin dermatitis (Conti et al. 2012). Some topical drugs can be considerably absorbed through the skin, and lesional distribution can be similar to systemic photosensitivity.

Acute Patterns of Drug Photosensitivity

Immediate Reactions

Immediate urticarial reactions, like photocontact urticaria, have been described with chlorpromazine (Lovell et al. 1986) and with 5-aminolevulinic acid used in photodynamic therapy (Kerr et al. 2007).

Some phototoxic drugs, like amiodarone and benoxaprofen (already removed from the market), induce immediate prickling and burning with transient erythema.

Immediate burning upon sun exposure followed by well-limited painful oedema and erythema during a few days, mimicking erythropoietic porphyria, is being described in more than 50 % of patients under vemurafenib treatment for metastatic melanoma (Rinderknecht et al. 2013). Photosensitivity can be highly limitative but can be prevented by sun avoidance or sun protection, extending to the long UVA.

Acute Photosensitive Dermatitis

Exaggerated sunburn that develops within 12–24 h of sun exposure is the main presentation of drug phototoxicity (Fig. 23.1). Non-pruritic erythema with sharp limits can be associated with vesicles and bullae and progress to desquamation in large epidermal sheets within the next days and, thereafter, to residual hyperpigmentation.

In acute drug photoallergy, confluent or non-confluent eczematous lesions or erythema multiforme-like lesions on photoexposed sites (Fig. 23.2), with frequent extension to covered areas, are mostly observed. In the case of photoallergy to piroxicam, pompholyx is often associated with non-confluent papular or vesicular facial lesions (Serra et al. 2008).

Subacute Patterns of Drug Photosensitivity

Photosensitivity may develop within days or weeks after exposure to the drug and the sun. Some clinical patterns evoke mainly a phototoxic reaction, like pseudoporphyria, photoonycholysis, hyper- or hypopigmentation, telangiectasia and purpura, whereas annular lesions may suggest a drug-induced cutaneous subacute LE.

Pseudoporphyria

Drug-induced pseudoporphyria resembles porphyria cutanea tarda or pseudoporphyria associated with haemodialysis, both clinically and on histopathology (bullae formation below the lamina densa). It develops within weeks to months as chronic skin fragility with flaccid bullae on non-inflamed exposed skin, occasionally progressing to milia. Pseudoporphyria occurs in individuals with no inborn error in porphyrin metabolism and no increase of endogenous porphyrins, although some drugs like voriconazole may transiently increase uroporphyrin levels.

Pseudoporphyria was initially described with nalidixic acid, furosemide and naproxen, predominantly in children (Ferguson 1999), but more recently, many other drugs have been associated with this phototoxic reaction: celecoxib (Cummins et al. 2000), ciprofloxacin (Schmutz et al. 2008), voriconazole, torasemide (Pérez-Bustillo et al. 2008), metformin (Lenfestey et al. 2012), finasteride (Santo Domingo et al. 2011) and imatinib (Timmer-de Mik et al. 2009). Pseudoporphyria represents a typical phototoxic reaction where the drug, as the uroporphyrin in the hereditary disease, probably induces phototoxicity through the production of singlet oxygen.

Photoonycholysis

Photoonycholysis is a typical pattern of phototoxicity. It presents as a half-moon distal onycholysis of one or several nails, most often as the single manifestation of phototoxicity (Fig. 23.4). It appears late (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 or doxycycline), psoralens and fluoroquinolones (Baran and Juhlin 2002).

There is no definite explanation for the single involvement of the nail: the nail bed, relatively unprotected from sunlight with less melanin, and the nail plate, working as a lens to concentrate the

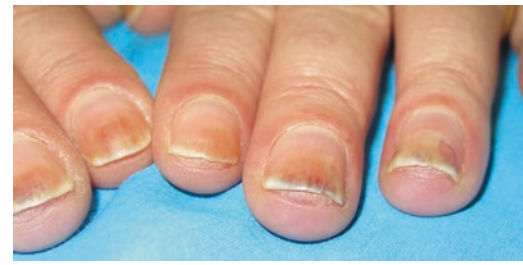

Fig. 23.4 Photoonycholysis from doxycycline

UVR, may enhance the inflammation and induce detachment of the nail plate from the nail bed.

Drug-Induced Cutaneous Lupus Erythematosus

In a recent multicentre database analysis of the European Society of Cutaneous Lupus Erythematosus, drug-induced cutaneous LE was shown to represent 6 % among 1,002 patients with cutaneous lesions and 13.2 % of those with the subacute variant of cutaneous LE (Biazar et al. 2013). This form of drug-induced subacute cutaneous LE is usually associated with photosensitivity and mild systemic manifestations of LE. More than 80 % of patients have anti-Ro/SSA autoantibodies, the hallmark of photosensitivity in LE.

Cutaneous lesions usually develop weeks or months after drug exposure (medium of 6 weeks) and can resolve on drug suspension, without scarring. They are annular or papulosquamous lesions, clinically and on histopathology similar to the idiopathic form of cutaneous subacute LE. Lesions are localized in photoexposed areas (face, neck, upper chest and arms) but also in usually UV-shaded areas. Erythema multiforme-like lesions or, seldom, chronic cutaneous LE with more infiltrated plaques on the face or V of the neck can also be related with drugs.

Subacute cutaneous LE was described initially in association with thiazide diuretics, calcium channel blockers, ACE inhibitors and more recently terbinafine, the drug associated with the highest odds ratio for this adverse event, and a long list of other drugs, namely, proton pump inhibitors, antiepileptics, TNF-alfa antagonists and anticancer taxanes, paclitaxel and docetaxel (Grönhagen et al. 2012; Lamond et al. 2013).

Dyschromia

Hyperpigmentation usually follows acute phototoxicity due to the residual melanocytic hyperpigmentation. In rare occasions, like in flutamide-induced photosensitivity, vitiliginous lesions with sharp limits occur after the acute reaction (Gonçalo et al. 1999). Dyschromia with solar lentigines and other signs of photoaging have been recently described with voriconazole and vandetanib (Malani and Aronoff 2008).

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. Some patients with lower phototypes also develop a golden-brown, slate grey or bluish colour on sun-exposed areas that persists longer after stopping the drug than residual melanocytic hyperpigmentation.

Other Clinical Patterns of Subacute Photosensitivity

Telangiectasia as a manifestation of photosensitivity has been reported with calcium channel blockers. 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. In rare cases, petechial purpura with sharp limits on the transition to the shaded areas was described with ciprofloxacin (Urbina et al. 2006).

Pellagra is associated with the prolonged use of isoniazid that needs niacin for its metabolism, and pellagroid reactions were reported with the anticancer agents, like 6-mercaptopurin and 5-fluoruracil.

Delayed and Late Effects of Photosensitivity

Patients that are chronically exposed to photoactive drugs can also develop accelerated photoaging, actinic keratosis and skin cancers, which, at least partially, can be explained by the photogenotoxic effect of some drugs.

Accelerated skin photoaging occurs with voriconazole, including in children, and presents as dyschromia, lentigines and actinic keratosis.

There is a consensual agreement on the dose-dependent increased risk of skin cancers after long-time therapeutic exposure to PUVA phototherapy. Apart from psoralens, drugs like naproxen, chlorpromazine and the fluoroquinolones, particularly lomefloxacin, augment DNA aggression induced in vitro by UV and increase epidermal neoplasia in animals

(Klecak et al. 1997). Also, in humans, potentially photosensitizing drugs, like diuretics and cardiovascular drugs, are being associated with increased cutaneous precancerous lesions, and recent reports correlate human short-term exposure (weeks/months) to voriconazole and vemurafenib with an increased risk of developing actinic keratoses, keratoacanthoma-like NMSC and, even, malignant melanoma.

Main Topical and Systemic Drugs Causing Photosensitivity

There is a large and increasing list of drugs inducing photosensitivity (Table 23.3), either when used topically or upon systemic exposure. Drugs, like piroxicam, induce photosensitivity both by topical and systemic exposure, whereas other drugs, like ketoprofen, frequently induce photoallergic contact dermatitis, whereas upon systemic exposure the cutaneous concentration is usually too low to induce photosensitivity.

Drugs manipulated in an occupational setting can induce photosensitivity: carprofen, an NSAID for animal use, induced photoallergic contact dermatitis in workers manufacturing the drug (Kiely and Murphy 2010), and photosensitivity has been reported in nurses and family members who smashed the tablets of chlorpromazine to give to their patients/relatives.

Topical drugs are, by far, responsible for most positive photopatch tests in studies from the south of Europe and in the recent European multicentre photopatch test study (The European Multicentre Study PhotopatchTest (EMCPPTS) Taskforce 2012). Main topical drugs that cause contact photosensitivity are the NSAIDs, namely, ketoprofen and other arylpropionic acid derivatives, etofenamate, benzydamine and phenothiazine derivatives used as antihistamines or muscle relaxants.

The main systemic drugs inducing photosensitivity are antimicrobials, particularly tetracyclines, fluoroquinolones, sulphonamides and antifungals, NSAIDs, phenothiazines and cardiovascular drugs.

Table 23.3 Main drugs causing exogenous photosensitivity

1. Antimicrobials
Tetracyclines[a] (doxycycline, minocycline)
Sulphonamides (sulfamethoxazole)
Fluoroquinolones (lomefloxacin,[a] ciprofloxacin[a])
Voriconazole,[a,b] griseofulvin[a]
Efavirenz, tenofovir
Faldaprevir
2. Nonsteroidal anti-inflammatory drugs (NSAIDs)
Arylpropionic acids:
Ketoprofen[c,d], tiaprofenic acid,[a] suprofen
Naproxen, ibuprofen, ibuproxam, carprofen[d]
Piroxicam[c,d], etofenamate[c,d]
Benzydamine[d]
Celecoxib, diclofenac[d]
Azapropazone, phenylbutazone, indomethacin
3. Phenothiazines
Chlorpromazine,[d] thioridazine
Promethazine,[c,d] isothipendyl chlorhydrate[d]
Chlorproethazine[c,d]
4. Targeted therapies
Vemurafenib[b]
Imatinib, vandetanib
5. Antidepressants
Clomipramine, imipramine, sertraline
6. Cardiovascular drugs
Amiodarone,[a] quinidine
Furosemide, torasemide and thiazide diuretics
7. Anticancer agents
Paclitaxel, docetaxel
Methotrexate, 5-fluoruracil
Dacarbazine
8. Miscellaneous
Psoralens[b]
Fenofibrate, simvastatin
Sulfonylureas, sitagliptin, metformin
Flutamide, finasteride
Pirfenidone
Porphyrin analogues for photodynamic therapy
Retinoids (isotretinoin)
9. Plants (used as drugs)[a]
Hypericum perforatum (St. John's wort)
Ruta graveolens (common rue)[d]
Kava extracts

[a]Mainly phototoxic
[b]An increase of actinic keratosis, NMSC and, occasionally, melanoma have been related with these drugs
[c]Mainly photoallergic
[d]Often also from topical exposure or airborne exposure, mainly in occupational settings

Antimicrobials

Tetracyclines

Systemic tetracyclines, particularly doxycycline and minocycline, are highly phototoxic, induce photoonycholysis and pseudoporphyria and, the latter, can also induce a bluish persistent pigmentation (Vassileva et al. 1998). A case of photoallergic reaction with positive photopatch tests was, nevertheless, described with doxycycline.

Quinolones

The fluoroquinolones induce phototoxic reactions, in some cases presenting as pseudoporphyria, as initially described for the first quinolone antibiotic, nalidixic acid. Ciprofloxacin was also responsible for purpura in photoexposed areas. Phototoxicity is particularly important and frequent (4–15 % of treated patients) with fleroxacin, lomefloxacin, sparfloxacin and pefloxacin and less frequent with ciprofloxacin, norfloxacin, ofloxacin and enoxacin (Ferguson 1999). The recommendation to take the drug by the end of the day, therefore reducing drug concentrations in the circulation and in the skin during midday, can reduce this phototoxic reaction.

Although in vitro and in vitro tests prove the high phototoxic potential of fluoroquinolones, photoallergy has also been reported with lomefloxacin and enoxacin. Reactivity in photopatch tests and in photoprovocation tests with very low UVA doses, cross-reactions with other fluoroquinolones (ciprofloxacin and flerofloxacin), positive lymphocyte stimulation tests and identification of drug-specific Th1 cells that recognize skin cells combined with UV-irradiated fluoroquinolone document photosensitivity is immune-mediated (Tokura et al. 2001).

Fluoroquinolones also photosensitize DNA and are, therefore, photomutagenic and photocarcinogenic. A young male patient from our hospital on long-term ciprofloxacin therapy for multiresistant tuberculosis developed chronic photosensitivity and highly aggressive recurring and metastatic squamous cell carcinomas of the face (personal experience).

Sulphonamide and Derivatives

Sulphonamide antibacterials, as well as sulpha drug analogues (thiazidic diuretics, hypoglycaemic sulfonylureas and celecoxib) and dapsone (diaminodiphenylsulfone), have been reported to cause photosensitivity within the spectrum both of UVB and UVA. This side effect is not so frequent with cotrimoxazole (Vassileva et al. 1998).

Antifungals

Griseofulvin is a known phototoxic drug and can aggravate lupus erythematosus, as the more recent antifungal, terbinafine, which induces subacute lupus erythematosus in patients with anti-Ro/SSA antibodies.

Voriconazole, used mainly in patients with invasive aspergillosis or refractory candidiasis, therefore with immunosuppression from an underlying disease or from immunosuppressive drugs, is associated with severe photosensitivity, an adverse effect that is not extensive to other azole antifungals. Photosensitivity develops in susceptible patients, including children. Apparently it does not depend on the highly variable individual pharmacokinetic profile of the drug and its main metabolite (n-oxide voriconazole), on the drug-metabolizing capacity or on increased levels of endogenous porphyrins or retinoids. Cutaneous reaction is dependent on the broad UVA, extends to the visible solar spectrum, develops within 1–16 weeks of treatment and manifests as a burning sensation soon after sun exposure, with a sunburn-like reaction, cheilitis and erosions of the lower lip (Fig. 23.3), or as pseudoporphyria (Riahi and Cohen 2011). On relative short exposures, photoaging with solar lentigines and actinic keratosis develops, and these soon progress to multifocal invasive squamous cell carcinoma (Morice et al. 2010). Malignant melanoma has also been described in these patients.

Antiviral Drugs

Photosensitivity from antiviral drugs used in the treatment of HIV or HCV infection has been reported. Efavirenz induced mostly photodistributed papulosquamous annular lesions within a few

days or weeks of treatment. The combination of faldaprevir and deleobuvir caused photosensitivity in more than a quarter of patients involved in controlled clinical trials (Zeuzem et al. 2013).

Nonsteroidal Anti-inflammatory Drugs

Benoxaprofen, marketed between 1980 and 1982, called the attention to photosensitivity from this class of drugs, and this adverse event was reported with other arylpropionic derivatives (carprofen, naproxen, suprofen, tiaprofenic acid, ketoprofen and ibuprofen) and NSAIDs from other groups (azapropazone, diclofenac, piroxicam, phenylbutazone, celecoxib, benzydamine and etofenamate). The in vitro and in vivo phototoxic potential has been documented particularly for tiaprofenic acid, with phototoxic reactions in more than half patients tested with tiaprofenic acid (5 % pet) and 5 J/cm^2 of UVA (Gonçalo et al. 1992), but in other studies tiaprofenic acid was typically photoallergic (Pigatto et al. 1996), therefore calling the attention to the concomitancy of both patterns of photosensitivity with the same drug.

Most topically applied NSAIDs are absorbed through the skin and can cause distant lesions, resembling systemic photosensitivity. Benzydamine, widely used in the oral or genital mucosa, causes photosensitivity at distant sites. When used in the mouth, benzydamine can induce cheilitis and chin dermatitis as a manifestation of photoallergy, and when used in a vaginal solution, hand dermatitis has occurred.

Ketoprofen

Ketoprofen, particularly when used topically in a gel formulation, is responsible for severe photoallergic reactions, often with oedema, bullae or erythema multiforme-like reactions, extending well beyond the area of application. Reactions may recur on sun exposure with no further drug application, as the drug or its metabolites persist in the skin for several days (>2 weeks) (Sugiura et al. 2000). There are also cases of connubial or by proxy contact dermatitis, namely, from the contaminated hands of the dance teacher, reactions induced by contact with contaminated objects, even clothes after being washed, or from exposure to cross-reactive chemicals, like benzophenones or octocrylene in sunscreens or benzophenones from magazine inks.

Although such a high frequency might suggest phototoxicity, the clinical pattern with erythema multiforme, positive lymphocyte stimulation tests with ketoprofen-photomodified cells, animal studies with absence of phototoxic potential, the capacity to photosensitize and transfer photoallergy by CD4$^+$ and CD8$^+$ T cells, in vitro activation and maturation of antigen-presenting cells by ketoprofen and UVA and characterization of a stable photoproduct – 3-hydroxy-ethyl-benzophenone – highly support a photoallergic reaction (Hino et al. 2008).

Cross-reactions occur between arylpropionic acid derivatives that share the benzophenone structure, namely, tiaprofenic acid and suprofen, and are not extensive to naproxen or ibuprofen. Cross-reactions are also common with the benzophenone UV filters, mainly oxybenzone, the UV filter octocrylene and the systemic hypolipemic agent, fenofibrate, that also induces systemic photosensitivity with cross-reactions with ketoprofen.

Patients with photoallergic contact dermatitis from ketoprofen have positive photopatch tests with 1 % ketoprofen, even if the patch is applied only for 1 h, and apart from the frequent cross-reactions in the photopatch tests (oxybenzone, octocrylene, fenofibrate), more than half of the patients also have positive patch tests to perfume mix I, particularly cinnamic alcohol (Pigatto et al. 1996). Moreover, many patients with contact allergy to cinnamic alcohol have positive photopatch tests to ketoprofen, a relation which is still not completely explained.

The analogues of ketoprofen, piketoprofen and dexketoprofen have a similar behaviour, in which concerns photosensitivity. A new topical formulation of ketoprofen, in plaster, may reduce the UV exposure of the drug but does not completely hinder this side effect of ketoprofen.

Piroxicam

Piroxicam is a known photosensitizer since the 1980s. Although there was some initial enigma around this photoallergy that usually developed with the first intakes of piroxicam, soon a relation was established with previous contact sensitivity to thiomersal (Cirne de Castro et al. 1991) and one of its main sensitizing moieties, thiosalicylic acid. Actually, upon low UVA irradiation, piroxicam decomposes and gives rise to a stable photoproduct structurally similar to thiosalicylic acid which is responsible for photosensitivity: in vitro UVA-irradiated solutions of piroxicam induce positive patch tests in patients with photosensitivity and individuals with positive patch tests to thiosalicylic acid, and animals sensitized by thiosalicylic acid develop positive photopatch tests to piroxicam.

Photoallergy from piroxicam can occur both from topical application and systemic use. It is becoming less frequent as this NSAID is replaced by newer drugs but it is still observed in Southern Europe (Cardoso et al. 2009), and a few cases were still found in the recent European multicentre photopatch test study.

Systemic photosensitivity develops within 24–48 h as an acute eczema involving diffusely the whole face or, often, as scattered erythematous papules and vesicles on the face and dorsum of the hands and pompholyx.

These patients do not react, neither on photopatch nor on drug rechallenge, to tenoxicam, meloxicam or lornoxicam, as these oxicams do not share the thiosalicylate moiety. Nevertheless, cross-reactivity between piroxicam and these oxicams occurs regularly in fixed drug eruption.

Other Drugs as Photosensitizers

Systemic phenothiazines (chlorpromazine and thioridazine), typically phototoxic, can induce lichenoid lesions with residual pigmentation, but most recent cases of photoallergy to chlorpromazine have been reported in caregivers who smash the tablets (Cardoso et al. 2009).

Promethazine, a highly phototoxic drug still used as a topical antipruritic, often induces photoallergic contact dermatitis. Another phenothiazine derivate, also used as a topical antipruritic, isothipendyl chlorhydrate, caused photoallergy with a positive photopatch test to chlorpromazine. Chlorproethazine, another phenothiazine marketed for some time in France and the UK as Neuriplege® cream for muscle pain (Genevrier, Antibes, France), was a frequent cause of photoallergic contact dermatitis in these countries.

The antiarrhythmic amiodarone induces erythema and a bluish-grey hyperpigmentation in sun-exposed areas due to the accumulation of drug metabolites in the dermis (Ferguson et al. 1985) The list of drugs causing photosensitivity is very large and always increasing, namely, with the recent inclusion of new kinase inhibitors in oncology, vandetanib, imatinib and, particularly, vemurafenib. With this drug more about 50 % of patients suffer burning and oedematous erythema on sun exposure (UVA) due to increased protoporphyrins and develop actinic keratosis, keratoacanthoma and squamous cell carcinoma, often as early as 8 weeks after initiating therapy for metastatic melanoma.

"Folk" Drugs as a Cause of Photosensitivity

Sometimes patients use "folk" medicines, mostly based on plant extracts, some of them rich in photoactive furocoumarins, which induce topical or systemic photosensitivity.

Since the antiquity, these substances have been used in the treatment of vitiligo and, more recently, in PUVA photochemotherapy.

Very occasionally, systemic photosensitivity develops upon oral exposure to furocoumarin-rich plants or their extracts, namely, to "homemade" infusions of St. John's wort (*Hypericum perforatum L.*) or to extracts commercialized in some European countries and used as a folk drug to treat depression (Fig. 23.5). Also, these infusions are occasionally used topically as a "folk medicine" with impressive adverse effects, as in a report where an infusion of *Ruta graveolens*, applied topically to relieve pain in fibromyalgia just before going into the sun, induced severe sunburn with bullae (Arias-Santiago et al. 2009).

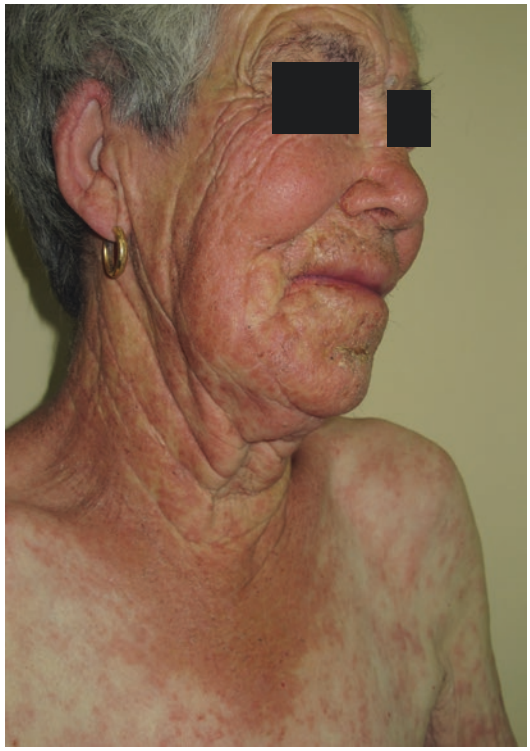

Fig. 23.5 Photosensitivity from consumption of infusion of *Hypericum perforatum* (St. John's wort)

Diagnostic Procedures in Drug Photosensitivity

Whenever a patient has a photosensitive eruption, a systematic inquiry for drugs should be conducted carefully.

Photopatch tests are indicated mainly for photoallergic contact dermatitis, but they can also be useful in the study of systemic drug photosensitivity. The recommended European baseline photopatch test series includes many drugs, namely, ketoprofen, etofenamate, piroxicam and benzydamine and also piketoprofen, dexketoprofen, ibuprofen, diclofenac, fenofibrate and chlorpromazine in the extended series (Gonçalo et al. 2013). Any other topical or systemic drug suspected of causing photosensitivity may be tested according to the general standardized procedures of photopatch testing. Briefly, allergens 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/cm2 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. Photopatch tests results have to be carefully interpreted. 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. If the reaction is mainly erythema and oedema, 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. 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.

In systemic photosensitivity, apart from photopatch tests, photoprovocation with irradiation after drug exposure or the calculation of the minimal UVA/B erythema dose when exposed to the drug and after drug withdrawal, may help identify the culprit.

In phototoxic reactions, both photopatch and photoprovocation tests are positive in the great majority of tested individuals; therefore, they are not particularly useful for confirming the aetiology of a phototoxic reaction, but they can disclose a hidden photoallergy.

General Principles of Treatment

Drug suspension and sun avoidance are recommended to resolve drug photosensitivity. When the drug is essential and life-saving, when there is no alternative drug or the alternative drug is not adequate, sun avoidance, protection from clothing and a broad-spectrum sunscreen that covers the UV spectrum of photosensitivity (mainly

within the UVA) may be adequate to improve photosensitivity. This protective effect of sunscreens can be helpful particularly in phototoxic reactions, as shown for voriconazole, vemurafenib and amiodarone. Broad-spectrum sunscreens may reduce both acute and long-term effects of photosensitivity, like photoaging and photocarcinogenesis, but they should always be associated with other sun-avoiding measures. Moreover, they should be recommended as preventive measures from the initiation of therapy with known photosensitive drugs. Nevertheless, it is important to recognize that chemical UV filters represent an important cause of contact photosensitivity, particularly in patients with previous dermatoses.

In cases of acute photoallergy from topical or systemic drugs, suspension of the culprit drug and sun avoidance will not resolve the skin lesions within a short time, and, therefore, active treatment may be necessary. Topical corticosteroids, in a formulation and potency adapted to the localization and severity of the dermatitis, may be prescribed for a few days. In severe reactions, as often observed with topical ketoprofen and systemic piroxicam, an additional short course of oral corticosteroids (24–32 mg of methylprednisolone, or equivalent, for a few days followed by a quick dose tapering) may be necessary to reduce acute symptoms and skin lesions.

In acute phototoxicity, presenting mainly as exaggerated acute sunburn, the efficacy of corticosteroids is highly questioned. Emollients and further photoprotection are advised for some time after resolution of acute photosensitivity.

Conclusion

Phototoxic, photoallergic and overlapping photosensitive reactions are still a frequent problem. They have a highly polymorphic clinical presentation, with different time courses and late consequences. Different responsible agents depend on geographic areas and, over time, depend on 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.

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