

Fotossensibilidade Induzida por Fármacos

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RESUMO – A fotossensibilidade induzida por fármacos traduz uma resposta cutânea anormal à luz em indivíduos expostos a um fármaco, os quais, na sua ausência, tolerariam o mesmo grau de fotoexposição. Pode ocorrer como uma reação aguda ou retardada, assumindo características clínicas polimórficas que variam desde a queimadura solar exagerada até aspectos de fotooncolise, pseudo-porfíria, pigmentação, eczema agudo e lúpus eritematoso cutâneo. Os autores descrevem os fármacos mais frequentemente envolvidos neste tipo de reações e as formas clínicas mais frequentes e discutem o possível contributo destes fármacos na potenciação da fotocarcinogénese. O reconhecimento destes padrões clínicos de fotossensibilidade e dos fármacos responsáveis é fundamental para a evicção do fármaco causal e consequente melhoria ou resolução da reação de fotossensibilidade.

PALAVRAS-CHAVE – Dermatite Fotoalérgica; Dermatite Fototóxica; Fotossensibilidade/induzida quimicamente; Pele/efeito de medicamentos.

Drug-Induced Photosensitivity

ABSTRACT – Drug-induced photosensitivity is an abnormal skin reaction to light in individuals exposed to a drug, whom, in the absence of the culprit drug, would tolerate the same amount of light exposure. It can present as an acute or delayed clinical picture, with polymorphic features ranging from an exaggerate sunburn to acute eczema, photoonycholysis, pseudo-porphyrria, pigmentation or cutaneous lupus erythematosus. The authors describe the drugs involved in these photosensitivity reactions and their main clinical pictures and discuss the possibility that these drugs can enhance photocarcinogenesis. Clinical recognition of these clinical patterns is of outmost importance in order to avoid the culprit drug and consequently improve or resolve photosensitivity.

KEY-WORDS – Dermatitis, Photoallergic; Dermatitis, Phototoxic; Patch Tests; Photosensitivity Disorders/chemically induced; Skin/drug effects.

1. INTRODUCTION

Drug photosensitivity can be defined as an abnormal cutaneous reaction to light (usually ultraviolet radiation (UVR), especially UVA) occurring in the setting of drug exposure.^{1,2}

One can, in theory, categorize drug photosensitivity by its pathomechanisms as immune-mediated (mostly photoallergy) or non-immune mediated (phototoxicity). Most immune-mediated reactions present as an eczematous eruption whereas classical phototoxicity is described as an acute sunburn. Both are predominant in sun-exposed skin, although the eczematous

pattern tends to be more widespread. There are, however, instances in which both types of reactions are intertwined and cannot be separated, both in their clinical features and underlying pathomechanisms. Furthermore, there are other examples of drug-induced photosensitivity, often overlooked and under diagnosed. That is the case of drug-induced lupus erythematosus (LE)³ or drug-induced non-melanoma skin cancer (NMSC). In the latter case, there has been increasing evidence for the role of widely prescribed photoactive drugs in the development of actinic keratosis and NMSC.⁴⁻⁷

More than 300 drugs, topical or systemic, can cause

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photosensitivity and this list continues to grow, as new drugs enter the market and patients' complexity increases. This paradigm is evident in HIV infection, where photosensitivity inherent to the disease blends with the added risk of photoactive drugs (as efavirenz and tenofovir).⁸

2. BASIC CONCEPTS IN DRUG PHOTOSENSITIVITY

Most drug photosensitivity reactions occur within the spectrum of UVA wavelength, although some can extend to UVB or visible light, generally from natural sun exposure. Artificial light, as used in UV lamps in aesthetic, therapeutic or occupational setting may also be involved. For drug-induced photosensitivity, however, the depth of penetration achieved by UVA is paramount in the elicitation of the reaction.⁹

Classically, drug photosensitivity is divided in **photoallergy** and **phototoxicity** (Table 1). **Photoallergy** is an immune-mediated reaction involving T-cell-dependent mechanisms and can result in photoallergic contact dermatitis or systemic photoallergy. In typical photoallergic reactions, the energy from the photon converts the drug into an unstable photoproduct, able to combine with an endogenous peptide forming a hapten or an antigen. Dendritic cells uptake this antigen and pair it with HLA molecules, carry it to the skin-draining lymph nodes, where, in the presence of cytokines and co-stimulatory molecules, they can stimulate and eventually sensitize naïve T cells. The resulting drug-specific T-cells will be mostly responsible for the effector response.¹⁰

These reactions develop only in a limited number of individuals and need previous sensitization. After a certain threshold, they are not dose-dependent and can develop even with low UV exposure. They resemble mostly eczema, with a



Figure 1 - Photoallergy reaction to St. John's Wort infusion. Note the eczema spreading to non-photoexposed areas.

predominant localization on sun-exposed areas but they can spread to non-exposed sites (Fig. 1). There can be cross-reactivity with structurally similar drugs. Histology reveals dermal

Table 1 - Distinction between phototoxicity and photoallergy

	PHOTOXICITY	PHOTOALLERGY
Frequency	Moderate to High	Low
Latency period / sensitization	None	Yes
UV doses / photosensitizer	High	Low
Cross-reactions	No	Yes
Basic morphology of lesions	Sunburn; Monomorphic	Eczema, erythema-multiforme-like
Limits	Sharp	Diffuse
Covered areas	Not involved	Possibly involved
Resolution	Fast	May recur; Persistent reactors
Residual hyperpigmentation	Yes	Usually not
Histology	Sunburn cells	Eczematous dermatitis
Pathomechanism	DNA damage/cell death ROS* production Inflammation	Type IV hypersensitivity to photoproducts

*ROS – reactive oxygen species

and epidermal T-cell infiltration and spongiosis with formation of vesicles.¹¹

Phototoxicity, by definition, does not involve specific immune mechanisms and is caused by the presence of an abnormal chromophore in exaggerated amounts in the skin. This chromophore can be either the drug itself, a drug metabolite or an endogenous chromophore induced by the drug. When excited by an UV photon, the chromophore's energy increases, entering a singlet state (a short-lived excited state) or a triplet state (a more stable, biologically active and long-lived state). These molecules then react with neighbouring molecules in a photodynamic reaction, leading to disruption of lipidic cell membranes and changes in the aromatic aminoacids of pyrimidine bases of DNA and RNA. Free radicals are also formed resulting in the damage of cellular organelles and ultimately, cytotoxicity. Inflammatory cytokines such as IL-1, IL-6, TNF-alpha and other inflammatory mediators such as prostaglandins and leukotrienes also contribute to this inflammatory response.^{1,9,12}

Typically, these are the most frequent reactions, developing in any individual as long as there is enough photosensitizer and sun exposure. They can occur on a first contact, with no particular aggravation on further contacts. Clinically they resemble acute sunburn with well-demarcated erythema exclusively on sun-exposed areas, resolving with hyperpigmentation. There is no cross-reactivity with other drugs and histology shows apoptotic keratinocytes (sunburn cells).¹¹

However, even though the mechanisms of photoallergy and phototoxicity are well established there are overlapping mechanisms as well as clinical manifestations. In fact, many drugs can induce **photoallergic and phototoxic reactions**. For example, the phototoxic furocoumarins, contained in plant extracts that are used in "folk medicine" or during photochemotherapy, can induce photoallergy.¹³ The same is true for promethazine and lomefloxacin, which have a well-established phototoxic potential but can also elicit photoallergic reactions.¹⁴⁻¹⁶

Less commonly, other mechanisms of photosensitivity can be considered, some immune-mediated like drug-induced LE while others are more phototoxic in nature, namely pseudoporphyria, photoaging and photocarcinogenesis.

3. CLINICAL FEATURES OF DRUG PHOTOSENSITIVITY

Photosensitivity can result from systemic uptake or topical application of drugs. Cutaneous lesions can vary from urticaria through eczema, subacute LE, vitiligo-like depigmentation, dyschromia, NMSC to acute sunburn^{1,17} (Table 2). The timeframe between drug introduction and beginning of skin findings can range from a few minutes (in vemurafenib-induced photosensitivity, for example) to years (in NMSC from voriconazole). Most photoallergic and phototoxic reactions, however, occur 1 to 2 days after introduction of the drug and sun exposure. For pseudoporphyria, drug-induced LE and photoonycholysis, it may take several days to weeks.

3.1 Systemic Photosensitivity

From a clinical standpoint, it is useful to divide patterns of drug-induced photosensitivity in acute, subacute and delayed reactions, since, as we have established previously, they can overlap in their pathomechanisms.

3.1.1 Acute Reactions

In **acute photoallergy from systemic drugs** lesions are mainly confluent or non-confluent eczematous patches in photo-exposed areas but can sometimes resemble erythema multiforme.^{18,19} They usually involve, in a symmetrical distribution, the face and forehead, V-shaped area of the neck and upper chest, dorsum of the hands and forearms. The shaded areas of the face (upper eyelids, upper lip, deep furrows), retroauricular and submentonian regions are usually spared. In more extensive sun exposure, large body folds, like the axillae, groins, finger webs and covered areas (clothes, watch string, shoes) are also usually spared. This is especially important

Table 2 - Clinical patterns of photosensitivity

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

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when distinguishing systemic photoallergy from airborne dermatitis, in which the shaded areas typically spared in exposure to photoactive drugs can be involved in airborne drug exposure, for example in nurses or other care-givers who crash tablets.

A slightly different distribution of lesions can occur, for example, in car drivers, who only expose the left side of body, giving rise to an asymmetrical pattern of sun-exposure. Furthermore, lesions can be found only on the lower lip, because of its higher exposure and thinner stratum corneum.²⁰

Most **systemic phototoxic reactions** occur between 12-24 hours after sun-exposure and resemble acute sunburn, with sharply delimited erythema that can progress to vesicles and bullae and later to desquamation in large epidermal sheets. Residual hyperpigmentation is frequent.

Some phototoxic drugs, however, can induce immediate prickling and burning with transient erythema¹ (amiodarone, for example – Fig. 2). Immediate burning is also seen with more than 50% of patients under vemurafenib treatment for metastatic melanoma.²¹ This can be prevented by sun avoidance and sun protection extending to the long UVA.^{22, 23}



Figure 2 - Amiodarone-induced erythema. Note the sparing of the wrinkles.

3.1.2 Subacute Reactions

These reactions usually take several days to weeks to develop, and mainly evoke phototoxic mechanisms as in pseudoporphyria, photoonycholysis, dyschromia, telangiectasia and purpura, whereas annular lesions may suggest drug-induced subacute cutaneous LE.

Drug-induced pseudoporphyria is clinically and histological indistinguishable from classical porphyria cutanea tarda, presenting with chronic skin fragility and flaccid bullae on non-inflamed, sun-exposed skin, occasionally progressing with the formation of millia. It usually develops within weeks to months after drug exposure. This pattern was described initially with nalidixic acid, furosemide and naproxen¹ but it has been recognized more recently with celecoxib,^{24,25} ciprofloxacin,²⁶ voriconazole,^{27,28} torsemide,²⁹ metformin,³⁰ finasteride³¹ and imatinib.³²⁻³⁴

Pseudoporphyria occurs in individuals with no inborn error in porphyrin metabolism and as such, no elevation in endogenous porphyrins is detected, apart from occasional transient increase of uroporphyrins with voriconazole.³⁵

Drug-induced cutaneous lupus erythematosus seems to be the consequence of the exaggerated expression of the Ro/SSA antigen on the surface of keratinocytes in the presence of the drug, however, the precise mechanisms underlying this reaction are not known.³⁶ Annular lesions are clinically and on histopathology similar to idiopathic form of subacute cutaneous LE and are located in photoexposed areas and also in usually UV-shaded areas.^{37,38}

Drug-induced subacute cutaneous LE usually develops weeks or months after drug exposure and is associated with a long list of drugs,³⁹ namely thiazide diuretics, calcium channel blockers, ACE inhibitors,³⁶ but particularly with terbinafine^{3,39} – the drug with the highest odds ratio for this event.³⁹



Figure 3 - Minocycline-induced photoonycholysis.

Photoonycholysis refers to the half-moon distal onycholysis of one or several nails, described usually 2-3 weeks after exposure to tetracyclines (doxycycline)⁴⁰ (Fig. 3), psoralens and fluoroquinolones.⁴¹ Although there is no definite explanation for this peculiar presentation of photosensitivity, most authors point out that the nail plate is relatively unprotected from sunlight (since it displays less melanin) and suffers from augmentation of sun exposure through the nail plate, acting like a lens through which concentrated UVR can enhance inflammation and result in nail detachment.⁴⁰⁻⁴²

Dyschromia can result from residual hyperpigmentation following an acute phototoxicity (Fig.4) and from photoaging (enhancement of solar lentigines) induced by some drugs (voriconazole, vandetanib^{43,44}). The accumulation of photoactive



Figure 4 - Residual hyper and hypopigmented lesions in fenofibrate phototoxicity.

drugs or their metabolites in the dermis may also lead to dyschromia, as is the case for amiodarone,⁴⁵ minocycline^{46,47} and phenothiazines (especially thioridazine).¹ A golden-brown or slate grey, bluish colour on sun-exposed areas can even persist longer after stopping these drugs.

Other clinical manifestations of subacute photosensitivity include **telangiectasia** in sun-exposed areas reported for calcium channel blockers,¹ petechial **purpura** with sharp limits on the transition to the shaded areas for ciprofloxacin,⁴⁸ **pellagra** as a consequence of niacin consumption during prolonged therapy with isoniazid and **pellagroid reactions** reported for anti-cancer agents such as 6-mercaptopurine and 5-fluorouracil.⁴⁹

3.1.3 Delayed Reactions

Chronic exposure to photoactive drugs can lead to accelerated photoaging, actinic keratosis and skin cancers. Voriconazole can result in dyschromia, lentigines, actinic keratosis and squamous cell carcinomas, even in children,^{7,50} and there is consensual agreement on dose-dependent increased risk for skin cancers after long-time PUVA phototherapy.⁵¹ Naproxen, chlorpromazine and fluoroquinolones, especially lomefloxacin, can augment DNA aggression induced in vitro by UV and result in epidermal neoplasia in animals.⁵² In humans, potentially photosensitizing drugs, such as diuretics and cardiovascular drugs, are being associated with a rise in cutaneous precancerous lesions.^{4,6} For vemurafenib there is a known risk for developing actinic keratoses, keratoacanthoma-like NMSC and even new melanomas but, probably, this is independent of photosensitivity and mostly dependent on the activation of alternate signalling pathways after BRAF inhibition.^{21,22}

3.2 Topical Photosensitivity

Topical photosensitizers are responsible mostly for acute reactions. Generally, in phototoxic contact dermatitis lesions develop minutes to days after sun-exposure, and in photoallergic there is a delay of usually 24 to 48 hours after ultraviolet exposure.⁵³ Immediate urticarial reactions, like photocontact urticaria, have also been described with chlorpromazine⁵⁴ and 5-aminolevulinic acid used in photodynamic therapy.⁵⁵

Clinically, photoallergic contact dermatitis presents as an eczematous response, whereas phototoxic appears as erythema, oedema and bullous lesions. In both types of photocontact dermatitis, lesions are localized in sun-exposed skin where the drug has been applied. Nevertheless, distant lesions can be the result of accidental contact (such as kissing lesions in the inner thighs or inadvertent spread by hands or contaminated objects^{56,57}). Connubial dermatitis has been described for ketoprofen and benzydamine.^{20,58-61} Also, when the drug is used topically in the mouth lesions can manifest as lip and chin dermatitis.^{20,62} If the contact photoallergen is significantly absorbed through the skin, it can mimic the distribution of systemic photosensitivity.

Next to the topical NSAIDs, UV filters are the main topical photosensitizers,^{15,63} and given their importance, a brief overview of photoallergy to sunscreens evolution is noteworthy.

PABA (*p*-aminobenzoic acid) was initially the main responsible for photoallergy contact dermatitis although nowadays has been largely replaced and is only seldom used.⁶⁴ Oxybenzone (benzophenone 3) was introduced in the 1970 and 1980's but despite being replaced in many sunscreens currently, is still one of the leading causes of positive photopatch tests.⁶³ The reasons for the high level of positivity to benzophenone 3 are possibly the wide presence in cosmetic products and the cross-reactivity with other agents containing benzophenone nucleus, such as ketoprofen and fenofibrate.^{53,65}

Cinnamates and salicylates have also been responsible for photoallergic reactions although apparently in a lesser degree.⁶⁶ Octocrylene, as a result of its wider use and in higher concentrations, is being responsible for a raising number of cases, notably in children and in adults previously photosensitized to ketoprofen.^{65,67,68}

Concerning the newer UV filters, Mexoryl SX (terephthalylidene dicamphor sulfonic acid), Tinosorb S® (bis-ethylhexyloxyphenol methoxyphenyl triazine) and Tinosorb M® (methylene bis-benzotriazolyl tetramethylbutylphenol) photoallergies are rare, but Tinosorb M® is frequently responsible for contact dermatitis due to decyl glucoside.^{65,69-71}

As new UV absorbers are introduced, the incidence of photoallergic contact dermatitis and causative allergens is likely to evolve.

4. MAIN DRUGS CAUSING PHOTOSENSITIVITY

The list of photosensitizers is large and ever-growing and comprises drugs that can be used topically or systemically (Table 3). Sometimes, a drug can induce photosensitivity by both ways, as piroxicam, for example. Other drugs, like ketoprofen, frequently induce a photoallergic contact dermatitis with topical use but its concentration on the skin from systemic exposure is usually insufficient for inducing photosensitization.

Topical drugs NSAIDs, namely ketoprofen, etofenamate, benzydamine and phenothiazine derivatives are the main agents responsible for photoallergic contact dermatitis^{15,63,72-74} and, by far, responsible for most positive patch-tests in southern Europe^{15,72-74} as recently shown also in a multicentre european photopatch test study (The European Multicentre Study

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Table 3 - Main drugs causing photosensitivity

SYSTEMIC PHOTOSENSITIVITY		TOPICAL PHOTOSENSITIVITY
Antimicrobials	Antidepressants	NSAIDs
Tetracyclines ^a (doxycycline, minocycline)	Clomipramine, imipramine, sertraline	Ketoprofen ^c
		Piroxicam ^c , etofenamate ^c
		Piroxicam ^c , etofenamate ^c benzydamine
		Diclofenac
Sulphonamides (sulfamethoxazole)	Cardiovascular drugs	Phenothiazines
Fluoroquinolones (lomefloxacin, ciprofloxacin) ^a	Amiodarone ^a , quinidine	Chlorpromazine
		Promethazine, chlorhydrate chlorproethazine
Voriconazole ^{a,b}	Furosemide, torasemide and thiazide diuretics	Plants (used as drugs)
Terbinafine, griseofulvina	Anti-cancer agents	<i>Ruta graveola</i> (common rue)
Efavirenz, tenofovir, faldeprevir	Paclitaxel, docetaxel	Photodynamic therapy agents
NSAIDs	Methotrexate, 5-fluoracil	5-aminolevulinic acid
Arylpropionic acids: Tiaprofenic acid ^a , suprofen Naproxen, ibuprofen, ibuproxam, carprofen ^a	Dacarbazine	
	Miscellaneous	
	Psoralens ^b , Fenofibrate, simvastatin	
Piroxicam ^{c,d}	Sulfonylureas, sitagliptin, metformin	
Celecoxib, diclofenac ^d	Flutamide, finasteride, pirfenidone	
Azapropazone, phenylbutazone, indomethacin	Retinoids	
Phenothiazines	Plants (used as drugs)^a	
Chlorpromazine ^d , thioridazine	<i>Hypericum perforatum</i> (St. John's wort)	
Targeted therapies		
Vemurafenib ^b , imatinib, vandetanib	Kava extracts	

^aMainly phototoxic; ^bAn increase of NMSC and actinic keratosis; ^cMainly photoallergic

Photopatch Test EMCPPS – 2012).⁶³ Although not considered a drug, UV filters are also an important source of photoallergic contact dermatitis as we have discussed previously.

Main systemic photosensitizers include antimicrobials, especially tetracyclines, fluoroquinolones, sulphonamides and antifungals, NSAIDs and cardiovascular drugs.

Antimicrobials, including **tetracyclines** and quinolones are among frequent photosensitizers. Doxycycline and less frequently minocycline are phototoxic, can induce photoonycholysis (Fig. 3), pseudoporphyria and for the latter there is also the risk of dyschromia, already covered in this article.^{1,40,47}

Quinolones, especially fluoroquinolones, can induce phototoxic reactions and pseudoporphyria.²⁶ This was evident for the first quinolone antibiotic – nalidixic acid,⁴⁷ but phototoxicity can also occur in up to 15% of patients treated with fleroxacin, lomefloxacin, sparfloxacin and pefloxacin, and less frequently for ciprofloxacin, norfloxacin, ofloxacin and enoxacin¹. Administering the drug at night, to reduce drug concentrations in

circulation during midday can diminish its phototoxic potential. Photoallergy with lomefloxacin^{14,16} (Fig. 5) and enoxacin⁴⁷ as well as cross-reactions with other fluorquinolones (ciprofloxacin and fleroxacin)^{75,76} have been described. Fluoroquinolones can also photosensitize DNA and have photomutagenic and photocarcinogenic properties.⁵²

Sulphonamides and sulpha-drugs, like thiazide diuretics, sulfonylureas and celecoxib, as well as dapsone (diaminodiphenylsulfone), have been reported to cause photosensitivity.^{47,77} Apparently, this side effect is not so frequent with cotrimoxazole.^{1,47}

Systemic **phenothiazines** (chlorpromazine and thioridazine) are not only phototoxic but can also induce lichenoid lesions with residual hyperpigmentation.¹ Promethazine, still used as a topical antipruritic, can induce both a phototoxic and photoallergic contact dermatitis.^{15,78} Other topical phenothiazines, like chlorproethazine used as a muscle relaxant and isothipendyl chlorhydrate, used as an antipruritic agent caused photoallergy and positive patch tests to chlorpromazine.^{79,80}



Figure 5 - Acute systemic photoallergy reaction induced by lomefloxacin.

Amiodarone, as previously discussed, can induce erythema (Fig. 2) followed by a bluish-grey hyperpigmentation in sun-exposed areas.⁴⁵

Antifungals comprise many agents with photosensitizing properties, namely **griseofulvin**, **terbinafine** and **voriconazole**. The first two can be found to aggravate lupus erythematosus, even inducing subacute lupus erythematosus in patients who develop anti-Ro/SS-A antibodies.^{3,39}

Photosensitivity to voriconazole is seemingly not extensive to other azole antifungals. This drug is used mainly in invasive aspergillosis or refractory candidiasis, generally in patients with previous immunosuppression, either from underlying diseases or from therapeutic immunosuppressants, therefore in individuals with a considerably risk for photosensitivity^{50,81} Photosensitivity from voriconazole can manifest as a sunburn reaction with cheilitis and erosions of the lower lip^{28,50,82} (Fig.6), as pseudoporphyria,²⁷ but also with photoaging with solar lentigines and actinic keratosis progressing into multifocal invasive squamous cell carcinoma,^{5,7,83,84} even with de-novo melanoma.⁸⁵

Antiviral agents, especially those used in the treatment of HIV and HCV infection, have been described as photosensitizing. Efavirenz, for example, induced papulosquamous annular lesions on photoexposed areas, only within a few days to weeks after initiation of treatment.^{86,87} Tenofovir, a newer anti-retroviral drug has also been reported as inducing systemic photoallergy, with positive photopatch tests.⁸⁸ This is especially important when you consider HIV infection in itself as a photosensitizing condition and a known risk-factor for a variety of photosensitive disorders.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a



Figure 6 - Voriconazole-induced cheilitis.

frequent cause of photosensitivity. This was initially seen with benoxaprofen, calling attention for this adverse event not only with this agent but to many others within this class (carprofen, naproxen, suprofen, ketoprofen, ibuprofen and tiaprofenic acid). Other NSAIDs, namely diclofenac, piroxicam, celecoxib, benzydamine and etofenamate were also documented as photosensitizers. For tiaprofenic acid, for example, in vitro and in vivo phototoxic potential was reported,^{89,90} but in other publications also photoallergic reactions were described,⁹¹⁻⁹³ underlining that both patterns of photosensitivity can be elicited by the same agent.

Most topically applied NSAIDs are absorbed through the skin and may cause distant lesions resembling a systemic photosensitivity. **Benzydamine**, used for oral or genital hygiene, causes photosensitivity at distant sites,¹⁵ as well as cheilitis and chin dermatitis or hand dermatitis caused by the application of the drug.^{15,20}

Ketoprofen may cause severe photoallergic reactions, with oedema, bullae and even erythema multiforme-like lesions.^{60,81,94-96} These extend well beyond the area of application, and can recur on sun-exposure even without further drug application,^{60,94} as the drug or its metabolite can persist in the skin for several days.⁹⁶ Cross-reactions with benzophenone and octocrylene in sunscreens⁶⁰ or benzophenones in magazine ink⁹⁷ have also been described. Cross-reactivity also occurs between arylpropionic acid derivatives that share the benzophenone structure, namely, tiaprofenic acid and suprofen, but is not extensive to naproxen or ibuprofen.

The analogues of ketoprofen, piketoprofen and dexketoprofen have a similar behaviour concerning photosensitivity.^{61,98} New topical formulations of ketoprofen in plaster aim to reduce UV exposure of the drug, but do not completely hinder this particular side-effect.

Piroxicam is a known photosensitizer since the 1980's, usually reacting on a first exposure because of its close relation to thiomersal⁹⁹ and its main sensitizing moiety of the molecule, thiosalicylic acid.¹⁰⁰ Photoallergy can occur both from topical and systemic use of the drug but, as this NSAID has been replaced by newer drugs, this side effect is becoming less

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Figure 7 - Positive photopatch test to benzydamine. Note that the erythema is only seen in the irradiated site.

frequent. However, a few cases were still found in the recent European multicentre photopatch test study.⁶³ Systemic photosensitivity develops within 24-48 hours as an acute eczema involving the whole face or as scattered erythematous papules and vesicles on the face and dorsum of the hands, often pompholyx-type.¹⁰¹⁻¹⁰³ Patients displaying this photoallergy do not react against tenoxicam, meloxicam or lornoxicam neither on photopatch nor on drug rechallenge, as these oxicams do not share the thiosalicylate moiety.¹⁰⁴ On the contrary, cross-reaction between piroxicam and other oxicams occurs regularly in fixed drug eruption.¹⁰⁵

More recently, the new **kinase inhibitors** and new anti-cancer drugs deserve a place among the drugs capable of eliciting photosensitivity. Vandetanib,¹⁰⁶ imatinib and in particular vemurafenib are known to cause phototoxic reactions. Regarding the latter, more than 50% of patients develop burning and oedematous erythema on sun-exposure^{22,23} and also actinic keratosis and squamous cell carcinoma, as early as within 8 weeks of starting therapy.²¹

Finally, "**folk**" medicines, mostly based on plant extracts, some of them rich in furocoumarins, can obviously result in systemic or topical photosensitivity, such as home-made infusions of St. John's wort (*Hypericum perforatum* L.)¹⁰⁷ (Fig. 1) and topically applied infusions of *Ruta graveolens*.¹⁰⁸

5. DIAGNOSTIC PROCEDURES IN DRUG PHOTOSENSITIVITY

A photosensitive eruption demands a careful and systematic review of all the drugs taken by the patient. Photopatch tests are indicated mainly for photoallergic contact dermatitis but can also be used to assess systemic drug photoallergy.^{17,109,110} The recommended European baseline photopatch test series includes ketoprofen, etofenamate, piroxicam and benzydamine, with the extended series covering also pike-toprofen, dexketoprofen, ibuprofen, diclofenac, fenofibrate and chlorpromazine,¹¹¹ but any suspected drug can be tested according to the general standardized procedures of photopatch testing.

Briefly, allergens are applied in duplicate on the back, followed by irradiation of only one of the sets at day 1 or day 2 with 5 J/cm² of UVA, whereas the other set is shielded from the light. Readings should be performed immediately after irradiation and also 48 and/or 72 h afterwards.¹¹²

Photopatch tests results have to be carefully interpreted: positive reactions in both sets mean contact allergy that can be photoaggravated if the reaction is 1+ more on the irradiated side. A photopatch test is positive when erythema and papules covering the whole test area is observed only in the irradiated set¹¹² (Fig. 7). If the reaction is mainly erythema and oedema, without pruritus and exclusively limited to the test chamber area, beginning shortly after irradiation, reaching its highest intensity by 24h and regressing in 48 to 72h, then it is probably a phototoxic event. If there is pruritic exanthema with vesicles, diffuse limits extending beyond the chamber area, with increasing intensity until 48-72h after irradiation, this is more suggestive of a photoallergic reaction.¹¹³

In systemic photosensitivity, oral photoprovocation with skin irradiation after drug exposure or with the calculation of the minimal erythema dose (MED) when exposed to the drug and after drug withdrawal may help to identify the culprit.

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

6. GENERAL PRINCIPLES OF TREATMENT OF DRUG PHOTOSENSITIVITY

Drug suspension and sun avoidance are recommended to resolve drug photosensitivity. If the drug is essential and life-saving, when there is no alternative drug or if the alternative drug is inadequate, sun avoidance, physical protection and a broad-spectrum sunscreen that covers the spectrum of UVA may be adequate to improve photosensitivity. For phototoxic reactions, this protective effect of sunscreen is particularly useful, as shown for voriconazole, vemurafenib and amiodarone.

Moreover, broad-spectrum sunscreen can be implemented as a preventive measure when initiating a known photosensitizer, however one must acknowledge that chemical UV filters represent an important cause of contact photosensitivity, particularly in patients with previous dermatoses.

In cases of acute photoallergy, suspension of the culprit drug and sun avoidance won't resolve the skin lesions within a short time and active treatment may be necessary. Topical corticosteroids may be prescribed for a few days and severe reactions may need an additional short course of oral corticosteroids with fast dose tapering.

Acute phototoxicity, presenting mainly as acute sunburn, may benefit greatly from emollients and photoprotection even for some time after the reaction, and the efficacy of corticosteroids is highly questioned in this setting.

7. CONCLUSION

Phototoxic, photoallergic and overlapping photosensitive reactions are still a frequent problem. They can exhibit clinical polymorphism, different time courses and late consequences. Culprit drugs often depend on geographic areas and prescription habits, changing also over time.

The dermatologist must be alert not only for the multiple clinical patterns that can result from photosensitivity but also for the many drugs that can cause it. A thorough review of all systemic and topical agents, including "folk" medicine, should be conducted and complementary tests such as photopatch tests, phototests and photoprovocation may contribute to a final etiologic diagnosis. These proceedings may finally allow adequate patient advice concerning further eviction of the photosensitizer and related chemicals and greatly improve the patient's quality of life.

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ASSESS WHAT YOU HAVE LEARNED

1. Which of the following features is not characteristic of a photoallergic reaction?

- a) Immune-mediated reaction involving T-cell dependent mechanism
- b) Resolves with hyperpigmentation
- c) Onset even with low UV exposure
- d) Clinically resembles eczema that is predominant on sun-exposed areas but can spread to non-exposed sites

2. Which of the following features is not characteristic of a phototoxic reaction?

- a) More frequent than photoallergy
- b) Can develop on any individual as long as there is enough photosensitizer and sun exposure
- c) Cross reactions with other drugs may occur
- d) Clinically resembles acute sunburn

3. Which drug is most likely to induce subacute cutaneous lupus erythematosus?

- a) Terbinafine
- b) Hydrochlorothiazide
- c) Amlodipine
- d) Perindopril

4. Considering photocarcinogenesis, select the wrong sentence

- a) Voriconazole can result in squamous cell carcinoma even in children
- b) PUVA is not associated with increased risk for skin cancer
- c) Vemurafenib can result in *de novo* melanomas
- d) Diuretics are being associated with a rise in cutaneous precancerous lesions

5. NSAIDs are important photosensitizers. Select the correct sentence

- a) Systemic ketoprofen commonly induces photosensitization
- b) The new topical formulation of ketoprofen in plaster is effective in preventing photosensitization
- c) Piroxicam-induced photoallergy can occur from both topical or systemic use
- d) Piroxicam cross-reacts with tenoxicam, meloxicam or lornoxicam

6. Minocycline can be responsible for which reactions?

- a) Photoonycholysis
- b) Pseudoporphyria
- c) Dyschromia
- d) All of the above

7. Considering photopatch tests, select the wrong sentence

- a) Allergens are applied in duplicate on the back, followed by irradiation of only one of the sets at day 1 or day 2 with 5 J/cm² of UVA, whereas the other set is shielded from the light.
- b) Positive reaction in both irradiated and non-irradiated set of allergens means contact allergy
- c) A photopatch test is positive when erythema and papules covering the whole test area is observed only in the irradiated region
- d) Early reaction, with erythema, oedema and pruritus reaching its highest intensity by 24h and regressing in 48 to 72 h suggests photoallergy