DRUG-INDUCED PHOTOSENSITIVITY

FOTOSSENSIBILIDADE INDUZIDA POR FÁRMACOS **PT**

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ABSTRACT

Drug-induced photosensitivity is an abnormal skin reaction in individuals exposed to radiation and certain drugs. A literature review was carried out through a database search of Pubmed, Cochrane Library and Science Direct, in order to identify drugs that cause photosensitivity reactions and acknowledge the role of the pharmacist in the management and prevention of such reactions. Articles dated up to 2020 were included in English, Portuguese and Spanish.

The prevalence of photosensitivity reactions depends on factors such as the geographical area and prescription and use habits. Various drug classes, namely NSAIDs (ketoprofen and piroxicam), Antifungals, Antibiotics (tetracyclines, fluoroquinolones), Antihypertensive, Statins, Antiarrhythmics (amiodarone), Retinoids e Chemotherapeutics (vemurafenib), are among the most frequently associated with the induction of photosensitivity reactions. Chronic exposure to these drugs may be associated with an increased risk of photocarcinogenesis.

A wide range of drugs, including the ones not subject to medical prescription, may induce photosensitivity, meaning that additional photo-protection precautions must be applied to the patient. The role of the pharmacist plays an important part in the medical counselling, prevention and management of eventual cutaneous reactions associated to these therapeutics.

Keywords: *Photosensitivity, Drugs, Photoallergy, Phototoxicity, Photoprotection.*

RESUMO

A fotossensibilidade induzida por fármacos consiste numa reação cutânea anormal, em indivíduos expostos a radiação e a determinados fármacos. Procedeu-se a uma revisão da literatura através de pesquisa em base de dados como Pubmed, Cochrane Library e Science Direct, com o objetivo de identificar os fármacos promotores de reações de fotossensibilidade e reconhecer o papel do farmacêutico na gestão e prevenção das reações. Foram incluídos artigos publicados até 2020, inclusive, e escritos em língua inglesa, portuguesa e espanhola.

A prevalência das reações de fotossensibilidade depende de fatores como área geográfica e hábitos de prescrição e consumo. Várias classes farmacoterapêuticas, nomeadamente AINE (cetoprofeno e piroxicam), Antifúngicos, Antibióticos (tetraciclinas, fluoroquinolonas), Anti-hipertensivos, Estatinas, Antiarrítmicos (amiodarona), Retinoides e Antineoplásicos (vemurafenib), estão entre as mais frequentemente envolvidas na indução da fotossensibilidade. A exposição crónica a estes fármacos pode estar associada a um aumento do risco de fotocarcinogenese.

Um grande número de fármacos, incluindo Não Sujeitos a Receita Médica, podem induzir fotossensibilidade o que implica cuidados acrescidos de fotoproteção do doente. O farmacêutico tem um papel importante no aconselhamento, prevenção e gestão de eventuais reações cutâneas.

Palavras-chave: *Fotossensibilidade, Fármacos, Foto-alergia, Fototoxicidade, Fotoproteção.*

RESUMEN

La fotosensibilidad inducida por fármacos es una reacción cutánea anormal en personas expuestas a radiación y ciertos fármacos. Se realizó una revisión de la literatura mediante búsquedas en bases de datos como Pubmed, Cochrane Library y Science Direct, con el fin de identificar fármacos que promuevan reacciones de fotosensibilidad y reconocer el papel del farmacéutico en el manejo y prevención de reacciones. Se incluyeron artículos publicados hasta 2020 inclusive y escritos en inglés, portugués y español.

La prevalencia de reacciones de fotosensibilidad depende de factores como la zona geográfica y los hábitos de prescripción y consumo. Varias clases farmacoterapéuticas, a saber, AINE (ketoprofeno y piroxicam), antifúngicos, antibióticos (tetraciclinas, fluoroquinolonas), antihipertensivos, estatinas, antiarrítmicos (amiodarona), retinoides y antineoplásicos (vemurafenib), se encuentran entre los más frecuentemente implicados en la fotosensibilidad. La exposición crónica a estos fármacos puede estar asociada con un mayor riesgo de fotocarcinogénesis.

Una gran cantidad de medicamentos, incluidos los de venta libre, pueden inducir fotosensibilidad, lo que implica un mayor cuidado de la fotoprotección del paciente. El farmacéutico tiene un papel importante en la orientación, la prevención y el tratamiento de las reacciones cutáneas.

Palabras clave: *Fotossensibilidad, Fármacos, Fotoalergia, Fototoxicidad, Fotoprotección.*

INTRODUCTION

Photosensitivity is defined as a sensitivity reaction that occurs between the skin and radiation, which translates into an abnormal skin response (Gouveia, Gameiro, Coutinho, & Gonçalo, 2016). This reaction happens due to the presence in the skin of chromophores of endogenous or exogenous origin (Gonçalo, 2019). It can be classified into five categories: primary photosensitivity, exogenous photosensitivity, metabolic photosensitivity, exacerbated photosensitivity and genetic photosensitivity (Oakley, Badri, & Harris, 2020).

When photo reactive drugs are involved in the photosensitivity reaction, it is called drug-induced photosensitivity reaction. This reaction consists of an abnormal response to radiation in individuals who have been or are exposed to a given drug (Gouveia et al., 2016).

With the growing destruction of the ozone layer, the incidence of photosensitivity reactions is increasing, since the radiation that reaches the earth's surface is increasingly intense (Zuba, Koronowska, Osmola-Mańkowska, & Jenerowicz, 2016). Not only radiation from the sun, but also artificial lights, such as UV lamps, emit UV radiation and may be involved in photosensitivity reactions (Serra, Santiago, Gonçalo, & Figueiredo, 2011).

The list of drugs that can cause photosensitivity reactions depends on geographic and demographic factors, prescription and consumption habits, among others, and has been increasing with the discovery of new molecules (Gouveia et al., 2016). Geographically, epidemiological divergences can be a cause of different prescribing habits.

The objective of this scientific work is to identify the drugs that are frequently involved in photosensitivity reactions and recognize the importance of the pharmacist's role in preventing them and educating populations.

METHODS AND MATERIALS

The Pubmed, Cochrane Library and Science Direct online electronic databases were used to search for relevant literature on drug-induced phototoxicity or and photoallergy, published between 2000 and 2020, in Portuguese, English or Spanish language. Keywords, such as Photosensitivity, Drugs, Photoallergy, Phototoxicity, Photoprotection, were used. A total of 168 papers was selected based on title and abstract and thorough checking of reference lists for additional papers. After full-text analysis, 46 papers were considered more relevant for the present review. The search was carried out during the year 2019 and 2020.

RESULTS AND DISCUSSION

TYPES AND MECHANISMS OF PHOTOSENSITIVITY REACTIONS

In order for a reaction to occur between the skin and radiation, resulting in a response from the body, the radiation must penetrate the stratum corneum, be absorbed by chromophores (endogenous or exogenous) and initiate chemical reactions in the surrounding tissues (Mang, Stege, & Krutmann, 2006). Phototoxicity and photoallergy are two distinct types of reactions. A phototoxic reaction translates into an exaggerated inflammatory response after exposure to radiation, not being an immunological mechanism (Serra et al., 2011).

When the chromophore, present in the epidermis or dermis, absorbs energy from radiation, it is in an excited state. This state can be called singlet or triplet state (Elkeeb, Elkeeb, & Maibach, 2012). The excited state is unstable and therefore it only exists for a short period of time (Zuba et al., 2016). The return to the ground state is associated with a loss of energy due to radiation, heat or chemical reactions. The chromophore, when in its excited state, can use energy to undergo direct molecular changes such as isomerization, oxidation and breakage of double bonds, or it can transfer this energy to neighboring molecules, giving rise to free radicals that are dependent or not on oxygen (Figure 1). These radicals modify cell membrane lipids, protein amino acids and nucleic acid nitrogen bases (DNA and RNA), and may eventually activate other molecules (Serra et al., 2011). Reactive oxygen species and other "abnormal" molecules can be detected by intracellular sensors. This recognition induces the activation of intracellular signaling pathways such as NF-kB, MAPkinases and the Nrf-2 pathway, and also induces the activation of the inflammasome, which leads to the activation of inflammatory mediators, such as: prostaglandins (PG); interleukins (IL) 1,6 and 8; TNF-[] among other pro-inflammatory cytokines (Gonçalo, 2019).

This exaggerated inflammatory response is responsible for phototoxicity. If the body does not act in time with cell repair mechanisms to control the chain reaction, there will be cell damage and consequently cell death.

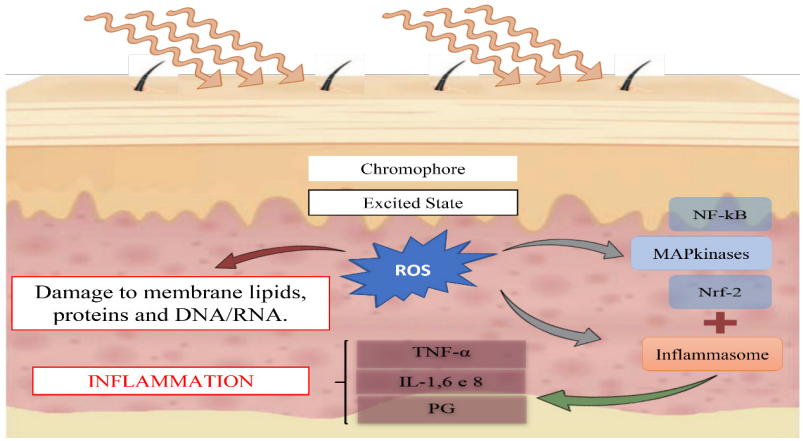

FIGURE 1: MECHANISM OF ACTION OF PHOTOTOXICITY, WITH FORMATION OF REACTIVE OXYGEN SPECIES.

A photoallergic reaction is a T cell-mediated hypersensitivity reaction against an allergen formed after exposure to UV radiation (Salgado et al., 2010). It requires prior sensitization to the photosensitizing agent and is a delayed hypersensitivity reaction because its onset time varies between 24 to 72 hours.

There are two possible mechanisms that lead to the photo-allergy reaction (Figure 2). In the first, and most often, the energy absorbed by the chromophore is used to transform it into a photoproduct. This photoproduct is a hapten that, when linked to a carrier molecule (protein), forms the so-called photo-allergen (Salgado et al., 2010). In the second mechanism, this absorbed energy favors the conjugation of the chromophore to a transporter (protein) through a covalent bond, forming a photo-allergen (Zuba et al., 2016). Allergen formation triggers a hypersensitivity reaction due to a T-cell mediated immune response (Mang et al., 2006).

Antigen-presenting cells, specifically dendritic cells (langerhans cells), upon capturing that allergen, become active and migrate to regional lymph nodes to sensitize T cells to the allergen in association with human leukocyte antigen (HLA) II antigens. Sensitized T cells, including memory and effector cells, will be activated and, on second contact, will circulate to sites exposed to radiation (Zuba et al., 2016).

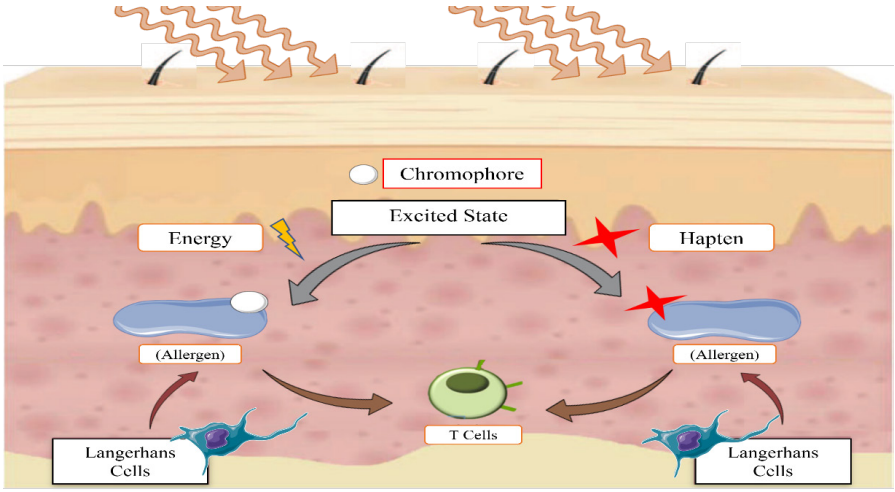

FIGURE 2: MECHANISM OF ACTION OF PHOTOALLERGY.

Classically, phototoxicity reactions are the most common and develop in a large number of individuals whereas photoallergy reactions occur only in a limited number of people (Serra et al., 2011). These reactions are dose-dependent, that is, they are dose-dependent on the photosensitizer and require moderate exposure to UV radiation. Photoallergy reactions are not dependent on the dose of photosensitizer and low exposure to UV radiation.

Despite the clear theoretical distinction (Table 1), in practice it is often difficult to distinguish a phototoxic reaction from a photoallergic reaction.

	PHOTOTOXICITY	PHOTOALLERGY
Frequency	High	Low
Latency period/sensitization	No	Yes
UV doses/photosensitizer	High	Low
Cross-reactions	No	yes
Basic morphology of lesions	Erythema similar to sunburn	Eczema Urticaria
Limits	Sharp	Diffuse
Covered areas	Not involved	Possibly involved
Resolution	Fast	May recur
Residual hiperpigmentation	Yes	No
Pathomechanism	DNA damage/cell death Inflammation	Type IV hypersensitivity to photoproducts

TABLE 1: THEORETICAL DIFFERENTIATION OF PHOTOTOXIC AND PHOTOALLERGIC REACTIONS (ADAPTED FROM SALGADO ET AL., 2010).

CLINICAL MANIFESTATIONS

The chemical and biological processes after radiation penetration and chromophore activation are complex and each chromophore can induce specific mechanisms that lead to different clinical manifestations of photosensitivity (Gonçalo, 2019).

Photosensitivity presents very varied clinical manifestations, sometimes with very typical or atypical patterns. These clinical patterns are conditioned by several factors such as, for example, the type of implicit photosensitivity reaction, the chromophore responsible for the reaction, the duration of the chromophore-radiation exposure, the location of the lesions, among others.

The initial symptoms of phototoxicity are tingling and erythema similar to mild sunburn. Photo-allergy reactions initially present with acute or subacute eczema (Serra et al., 2011). In general, each type of reaction has specific clinical characteristics (Table 2), however, there are other overlapping characteristics.

	PHOTOTOXICITY	PHOTOALLERGY
Clinical Manifestations	Exaggerated "sunburn"	Acute and subacute eczema
	Pseudoporphyria	Photoallergic contact dermatitis
	Photoonycholysis	Cheilitis
	Dyschromia	Urticaria
	Purpura	Lichenoid reactions
		Subacute or chronic lupus erythematosus

TABLE 2: PREDOMINANT CLINICAL PATTERNS BY TYPE OF PHOTOSENSITIVITY REACTION (ADAPTED FROM SERRA ET AL., 2011).

PHOTOSENSITIZING DRUGS

A large number of drugs are involved in phototoxicity and photoallergy reactions, with conclusive clinical and scientific evidence. For a rash to be drug-induced and to be considered photosensitive it must occur in a context of radiation exposure, the drug or its metabolites must be present on the skin at the time of exposure and they must be able to absorb incident radiation (Blakely, Drucker, & Rosen, 2019).

Drug-induced photosensitivity (DIP) can be caused by a topical or systemic agent. Topical agents are more likely to damage keratinocytes because they are more concentrated in the epidermal layer. Systemic agents are more phototoxic to mast cells and endothelial cells present in the dermis (Serra et al., 2011).

Regarding the hydrophilic and lipophilic characteristics of pharmacological agents, a hydrophilic drug mainly damages cell membranes, unlike a lipophilic drug that diffuses into the cell and destroys intracellular components such as liposomes, nucleus and mitochondria (Mang et al., 2006).

1. NON-STEROIDAL ANTI-INFLAMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAID) are a heterogeneous class of drugs that act by inhibiting the activity of the enzyme cyclooxygenase (COX). Its classification may differ, based on chemical structure, potency, selectivity of inhibition of different subtypes of COX, among others.

They are a class with a wide consumption worldwide and have a wide use, including as analgesics, anti-inflammatory and antipyretics (Blakely et al., 2019). Its high consumption has provided several reports of photosensitivity effects, being considered the most common cause of DIP. Their ability to cause an inflammatory skin reaction contrasts with their pharmacological ability to inhibit inflammatory responses (Mang et al., 2006).

The photosensitivity associated with NSAID became evident between 1980 and 1982 with the commercialization of benoxaprofen, a derivative of propionic acid (Serra et al., 2011). This drug was later withdrawn from the European market due to associated adverse effects and the high frequency of phototoxic reactions. Subsequently, all other propionic acid derivatives have been shown to be frequently associated with photosensitivity reactions (Gonçalo, 2011).

Photochemical studies have shown that NSAID phototoxicity is mediated mainly by reactive oxygen species and free radicals (Mang et al., 2006). Ketoprofen and piroxicam, despite not being the most sold drugs within this group, are the main causes of DIP. Both cause photoallergy with very particular clinical patterns of cross-reactivity (Gonçalo, 2011).

1.1 KETOPROFEN

Since 1985, ketoprofen has been associated with a number of reported cases of photosensitivity. This drug, especially when used topically, is known to cause photoallergic reactions (Serra et al., 2011). Sometimes these reactions can be severe, with the presence of edema, blisters and even lesions similar to erythema multiforme that go beyond the application area (Gonçalo, 2011).

Occasionally, relapses can occur only with exposure to radiation, without a clear re-exposure to the drug. This is because the drug can remain on the skin for at least 17 days (Sugiura, Hayakawa, Kato, Sugiura, & Ueda, 2000). Contact with contaminated surfaces such as garments or exposure to substances with possible cross-reactivity may also be a justification (Serra et al., 2011).

Although photoallergy reactions are the most common, ketoprofen may also be involved in phototoxicity reactions. The phototoxicity of ketoprofen can be explained by the production of oxygen free radicals, which are reactive with proteins and lipids (Nakajima, Tahara, Yoshimura, & Nakazawa, 2005). Other authors have shown that irritation caused by ketoprofen in the presence of radiation can cause erythrocyte photolysis, an indicator of cell damage (Zuba et al., 2016).

Ketoprofen has particular clinical patterns of cross-reactions. Considering its chemical structure, this drug has an aromatic ketone (benzophenone) in its constitution. Cross-reactions can occur between propionic acid derivatives, which share the benzophenone radical (tiaprofenic acid and suprofen), with the exception of naproxen and ibuprofen (Gonçalo, 2011). Other drugs, such as fenofibrate and amiodarone, can cause cross-reactions with ketoprofen as they present a radical similar to benzophenone in their chemical structure (Serra et al., 2011).

Photoallergic contact dermatitis is a typical clinical pattern for the use of the drug in question. According to Jenerowicz et al. (2011), 3 cases of photoallergic contact dermatitis were diagnosed after topical use of ketoprofen. All had skin lesions with eczema, restricted only to the area of application of the drug. The interval between the use of the drug and the onset of manifestations ranged from 2 to 60 days (Jenerowicz et al., 2011). Lozzi et al. (2020) reported 2 cases of photodermatitis associated with the use of systemic ketoprofen, in subjects who previously developed reactions to the drug via the topical route.

1.2 PIROXICAM

The photosensitivity associated with piroxicam has been known since 1983, the year in which the first associated case was reported (Zuba et al., 2016). Fjellner (1983) observed, on the skin of a woman exposed to radiation, erythematous eruptions with the presence of blisters after systemic treatment with piroxicam.

In the beginning there was no concrete explanation regarding the underlying mechanism, but later a relationship was established with the already known sensitivity to thimerosal. Effectively, under the action of UV radiation, piroxicam decomposes and gives rise to a photo-product structurally similar to thiosalicylic acid. This acid is the fraction of thimerosal responsible for the photoallergy caused by it and explains the cross-reactivity with piroxicam. Thus, individuals previously sensitized to thimerosal may develop photosensitivity, more specifically photoallergy, to piroxicam (Serra et al., 2011) (Gonçalo, 2011).

Other evidence supporting this cross-reactivity relationship includes positive patch tests to piroxicam in patients with a previously known allergy to thiosalicylic acid in the presence of UV radiation; reproduction of photosensitivity to piroxicam through animal models; and presence of lymphocytes stimulated with both thiosalicylic acid and piroxicam, after irradiation (Serra et al., 2011).

The photosensitivity caused by piroxicam has decreased in the last 20 to 30 years, possibly due to the decrease in medical prescriptions, which leads to a lower consumption of the drug, and in parallel to the discovery and increasing consumption of new NSAID (Gonçalo, 2019) (Serra et al., 2011).

Photoallergy can occur with both topical and systemic formulations (Gouveia et al., 2016). Systemically, it can manifest as an acute eczema diffusely involving the entire face or as erythematous papules and vesicles scattered over photoexposed areas such as the face and back of the hands.

2. TETRACYCLINES

Tetracyclines are a semi-synthetic group of broad-spectrum antibiotics and are considered to be one of the most frequent photosensitizing classes within antibacterials (Zuba et al., 2016). Tetracyclines can give rise to singlet oxygen radicals, which in turn cause oxidation that leads to cell damage. It is possible that phototoxic reactions associated with tetracyclines occur due to the drug's binding to melanin biopolymers and its accumulation in pigmented tissues (Rok et al., 2015).

Rok and collaborators (Rok et al., 2015) analyzed the effect of the tetracycline-solar radiation relationship on cell viability and melanin synthesis in normal human epidermal melanocytes. Cell viability decreases depending on the drug concentration and the body's defense systems undergo changes. Tetracycline by itself has no influence on melanin synthesis but in the presence of UV radiation it causes biochemical changes, such as oxidative stress inside melanocytes.

The typical clinical manifestations of photosensitivity to this pharmacological group are sunburn with or without the association of papules and blisters (Zuba et al., 2016) (Kuznetsov, Weisenseel, Flaig, Ruzicka, & Prinz, 2011). Photo-onycholysis can also occur, usually two weeks after drug administration.

3. FLUOROQUINOLONES

Fluoroquinolones (FQ) are a pharmacological group of antibiotics with a broad spectrum of action. Its chemical structure is based on the double ring system, either with a quinolone nucleus (nitrogen at position 1) or with a naphthyridine nucleus (additional nitrogen at position 8) (Eljaaly, Alkhalaf, Alhifany, & Alshibani, 2020).

When this group undergoes changes in its chemical structure, it can, consequently, affect its antibacterial action, toxicity and the risk of photosensitivity reactions (Zelmat et al., 2020). Photosensitivity is a known adverse skin reaction in this pharmacological group, which can cause various skin conditions.

FQ mainly cause phototoxic reactions, although there are some reports in the literature of photoallergic reactions (Zuba et al., 2016). A recently published study, with the aim of evaluating the different phototoxic potentials of FQ, suggested that the phototoxic potential of this pharmacological group depends on the drug-melanin interaction, its ability to affect melanogenesis and the pigmentation of melanocytes (Beberok et al., 2017).

Through the analysis of several studies, it was possible to establish a relationship between the chemical structure of FQ and the risk of photosensitivity. Zelmat et al. (2020) analyzed the relationship between the chemical structure of FQ and the rate of adverse effects, based on real data provided by Vigibase® database. The results confirmed that the high risk of photosensitivity is associated with the halogen present in the 8th position (Zelmat et al., 2020).

The FQ that contain a halogen at position 8 include sparfloxacin, lomefloxacin and clinafloxacin, and are considered to have the greatest phototoxic potential. Derivatives that contain a hydrogen in the same position include ciprofloxacin and levofloxacin and are considered to have the lowest phototoxic power. In contrast, those with a methoxy group in this position, such as moxifloxacin, are considered more photostable and less phototoxic (Blakely et al., 2019).

A meta-analysis evaluated the photosensitivity potential of lomefloxacin versus other fluoroquinolones. Lomefloxacin entered the market in 1990 and has since been used as a positive control in several studies. Its photosensitivity is attributed to the 8th position fluorine atom, which appears to increase its chemical changes and cytotoxicity (Eljaaly et al., 2020). In this meta-analysis, it was concluded that lomefloxacin has a significantly higher incidence of photosensitivity compared to other FQ.

The incidence and severity of reactions depends on the type, chemical structure of the drug and its derivatives. Phototoxicity induced by FQ can be manifested by sunburn-like lesions, edema, scaling, eczema with bullous eruptions and erythema (Beberok et al., 2017).

Photoallergy, despite being less frequent, is associated with lomefloxacin and ofloxacin (Serra et al., 2011).

4. ANTIFUNGALS

Voriconazole is a second-generation triazole antifungal with a broad spectrum of action, used to treat severe fungal infections (Blakely et al., 2019). Its use is associated with several skin reactions such as photosensitivity, photoaging and skin cancer (Goyal, 2015).

Although it is usually well tolerated, in a recent systematic review it was reported that it is the second most commonly reported drug to induce toxicity reactions (Kim et al., 2018).

In many cases, it is difficult to predict the photoreactivity potential of a molecule according to its chemical structure. In the case of voriconazole, its structure has several components that enhance the possible photosensitizing properties, such as the presence of a halogen atom and its polycyclic character. However, most azoles have similar chemical characteristics and are not associated with cases of phototoxicity (Epaulard et al., 2011).

A study on the UV absorption spectrum of voriconazole showed that the molecule responsible for its phototoxicity is possibly its active metabolite (N-oxide), since it absorbs UVA and UVB radiation (Murayama, Imai, Nakane, Shimizu, & Yamazaki, 2007).

The clinical patterns of voriconazole-induced reactions vary from classic patterns such as erythema and sunburn, to cheilitis, photo-onycholysis and pseudoporphyria (Blakely et al., 2019).

5. ANTIHYPERTENSIVE

Antihypertensive drugs are the most widely used therapeutic group, especially by the elderly (Zuba et al., 2016). The three main categories of antihypertensive drugs most commonly involved in photoinduced skin reactions are: diuretics, calcium channel blockers (CCB) and angiotensin receptor antagonists (ARA).

Thiazide diuretics were first marketed in 1950 and are the most commonly prescribed type of diuretics. Soon after its introduction on the market, photosensitivity reactions associated with its use began to be documented (Blakely et al., 2019).

Of the thiazide diuretics, hydrochlorothiazide is the drug with the most case reports in the literature associated with photosensitivity (Gomez-Bernal et al., 2014). Exaggerated sunburn, eczema, lichenoid lesions, and dyschromia are clinical patterns associated with hydrochlorothiazide photoinduction (Blakely et al., 2019) (Johnston & Coulson, 2002). Indapamide, although not associated with skin reactions, is associated with the induction of photoonycholysis (Rutherford & Sinclair, 2007).

Within loop diuretics, furosemide is a possible inducer of phototoxicity. Unlike thiazide diuretics, furosemide is associated with blistering rash (Blakely et al., 2019).

It is suspected that the possible photosensitizing character comes from a substituent, chlorine, which is present in the chemical structure of thiazide diuretics and furosemide. Chlorine dissociates with UV radiation and promotes reactions between lipids, proteins and DNA (Zuba et al., 2016).

Regarding CCB, amlodipine and nifedipine are examples from the dihydropyridine group that are associated with photosensitivity reactions. They are mainly associated with facial telangiectasia. Nifedipine is also associated with photodermatitis (Blakely et al., 2019).

Based on a retrospective study where cases reported between 1968 and 2014 were evaluated through Vigibase® database, it was concluded that there is a strong association between skin photosensitivity and the use of ARA. The reported cases analyzed occurred mainly with the use of losartan, irbersartan and valsartan (E. Viola, Coggiola, Agnes, Ugo, & Conforti, 2015).

6. AMIODARONE

Amiodarone is a drug belonging to the class III antiarrhythmics group used to prevent and treat ventricular arrhythmias and atrial fibrillation (Blakely et al., 2019). It has been associated with several adverse cutaneous reactions, including photosensitivity (Lozzi et al., 2020).

Amiodarone, including its active metabolite desethylmiodarone, accumulates in the skin where it can be detected at ten times higher concentrations in pigmented areas compared to non-pigmented areas (Lozzi et al., 2020). It has been shown that the drug in question is stored in secondary lysosomes linked to lipofuscin (intracellular pigment), as a consequence of phagocytosis of dermal macrophages.

During exposure to radiation, erythema, burning and/or immediate sunburn may occur. Amiodarone-induced photosensitivity is classified as exaggerated sunburn, hyperpigmentation, pseudoporphyria, and erythema (Zuba et al., 2016). Long-term exposure can induce a blue-gray pigmentation in areas exposed to solar radiation, which can be explained by the accumulation of the drug in lysosomes (Lozzi et al., 2020). Manifestations usually resolve months after stopping treatment (Blakely et al., 2019).

7. STATINS

Statins are HMG-CoA reductase inhibitors, a class of anti-dyslipidemics very commonly used to lower cholesterol levels. Cases of skin reactions, including photosensitivity, induced by the use of statins have been reported, although this is not a common adverse effect of this class of drugs (Zuba et al., 2016).

One study, based on photochemical and photophysical results, attributed the phototoxicity of atorvastatin to the formation of singlet oxygen via a photoproduct similar to phenanthrene. The degradation of atorvastatin by radiation gives rise to photoproducts resulting from the oxidation of the pyrrole-like ring. Another way is the stilbene-like structure of atorvastatin, which causes a cyclization process and leads to the formation of a photoproduct similar to phenanthrene (Montanaro, Lhiaubet-vallet, Iesce, Previtera, & Miranda, 2009).

Atorvastatin-induced photosensitivity has been reported to manifest as erythema with edema in the photoexposed areas (Blakely et al., 2019).

According to Viola et al. (2010), after the incidence of radiation, fluvastatin phototoxicity is mediated by the formation of a polycyclic photoproduct similar to benzocarbazole. In that study, it was concluded that fluvastatin and its photoproducts induce phototoxicity mainly in cell membranes.

8. RETINOIDS

Retinoids are a group of vitamin A derivatives and include the active substances tretinoin, isotretinoin, adapalene, acitretin, bexarotene, and tazarotene. They are available in topical and oral formulations and are mainly used in cases of severe acne and psoriasis.

Retinoids are known to be involved in photosensitivity reactions, however there is very little recent scientific evidence to support this (Blakely et al., 2019) (Fu et al., 2003).

Retinoid photosensitivity may be associated with the concomitant use of voriconazole. Tretinoin is metabolized by CYP450 isoenzymes and voriconazole as an inhibitor of these enzymes may potentiate the increase in retinol levels (Denning & Griffiths, 2001).

9. VEMURAFENIB

Vemurafenib is a BRAF enzyme inhibitor indicated for the treatment of melanoma with BRAF V600 mutation. In a study that included 520 patients and evaluated the cutaneous adverse effects of vemurafenib treatment, approximately 35 to 63% of patients had photosensitivity (Lacoutute et al., 2013).

In vitro studies support that vemurafenib-induced photosensitivity consists of phototoxic mechanisms with inhibition of DNA damage repair. Its hydrophobic characteristics favor that its toxicity is associated with damage to cell membranes and consequent damage to DNA repair mechanisms.

Several studies confirm that the photosensitivity of vemurafenib lies within the UVA spectrum. Heppt et al. (2020) confirmed that most BRAF inhibitors have a phototoxic potential after exposure to UVA radiation. Dummer (2012) also demonstrated that the photosensitivity induced by vemurafenib is dependent on UVA radiation, since the use of sun protection with UVA filters prevented the occurrence of photosensitive reactions.

Clinically, vemurafenib-induced photosensitivity initially presents as a feeling of heat, erythema with edema, and sunburn. Unlike other drugs, vemurafenib induces an immediate and direct reaction during exposure to UV radiation, characterized by a feeling of heat and sunburn, with possible edema (Eberlein, Hein, Biedermann, & Posch, 2020).

PHOTOCARCINOGENESIS

Radiation plays an important role in promoting photocarcinogenesis and in recent years the properties of various drugs and their carcinogenic capacity have been addressed. There are numerous drugs with distinct and well elucidated mechanisms that enhance the development of photocarcinogenesis, but, in contrast, there are still many drugs in which the mechanisms are not yet known (Gorman & Murphy, 2013).

Chronic use of drugs with photosensitizing properties and exposure to radiation can promote cutaneous photocarcinogenesis (Serra et al., 2011). Many phototoxic drugs generate free radicals (eg, ROS) and cause cell damage, also causing chromosomal damage in the presence of radiation such as photogenotoxicity and photomutagenicity, with consequent implications for photocarcinogenesis (Gonçalo, 2019).

Although free radical formation is a feature of photosensitivity reactions, subsequent chronic inflammation may be related to the development of photocarcinogenesis. That is, both oxidative stress and the resulting inflammatory responses are factors that contribute to and potentiate the risk of photocarcinogenesis (Kreutz, Abdel, Algharably, & Douros, 2019).

Several studies suggest the association between prolonged use of photosensitizing drugs and an increased risk of skin cancer. Pharmacological classes such as NSAID, antibacterials, antifungals, antihypertensives and antineoplastics are associated with photocarcinogenesis.

Through a case-control study, the association between the use of phototoxic drugs and the development of cutaneous melanoma (CM) was investigated. The results showed that the use of phototoxic drugs is associated with an increased risk of developing CM and that, of all drug classes analyzed in the study, FQ and NSAID presented the greatest evidence of this association (Siiskonen et al., 2013).

It is speculated that the possible carcinogenic characteristics of FQ may not be of significant importance in clinical practice, as they are generally prescribed for a short period of time. However, in this study this was not confirmed.

Li et al. (2017) analyzed the use of tetracyclines and the risk of skin cancer through a prospective study. The use of tetracyclines was associated with a risk of basal cell carcinoma (BCC) but was not associated with CM or squamous cell carcinoma (SCC).

Sheu et al. (2015) through a retrospective review, analyzed the incidence of phototoxic reactions and skin cancer in pediatric patients treated with voriconazole. They concluded that voriconazole-associated phototoxicity is relatively common and that its long-term use increases the risk of photocarcinogenesis. Miller et al. (2015) reported 2 cases of CM in patients with extreme photosensitivity during long-term treatment with voriconazole.

Regarding antihypertensive drugs, through a case-control study in Denmark, the use of antihypertensive drugs and the risk of photocarcinogenesis were investigated. The authors found a strong association between the long-term use of ARA and CM, and the use of diuretics and SCC. Associations with the other classes of antihypertensive drugs were inconclusive in this study (Schmidt, Schmidt, Mehnert, Lemeshow, & Sørensen, 2015). Bendinelli et al. (2019) also stated that the use of thiazide diuretics and the increased risk of skin cancer, more specifically SCC, seems to be related.

Gandini et al. (2018) also analyzed the association between the use of antihypertensive drugs and the risk of CM and concluded that there is a significant increase in risk with the prolonged use of CCB and β-blockers.

MANAGEMENT AND PREVENTION OF REACTIONS

The list of drugs, including non-prescription drugs, that induce photosensitivity reactions is wide, which is worrying and requires increased attention from health professionals, such as doctors, nurses and higher pharmacy professionals. A multidisciplinary approach is crucial for the correct identification and management of these situations. Indeed, diagnosis requires careful assessment. The patient's clinical history is essential, and it is important to understand the duration of the onset of photodermatosis, its distribution and evolution, and identify which topical and/or systemic drugs may be involved. To assist, patch tests such as photopatch test, phototest and photoprovocation test can be performed.

Once a rash occurs, if the discontinuation of the drug is not possible, there is a need to evaluate and implement other alternatives. In milder situations, the use of emollients and photoprotection may be recommended to alleviate symptoms, but in more severe cases there may be a need for topical or systemic treatment with antihistamines or corticosteroids (Blakely et al., 2019) (Moore, 2002).

Nevertheless, the mainstay of treatment is prevention as, in most cases, discontinuation of the photosensitizing drug(s) is not possible. Prevention essentially involves informing and alerting the patient of the possibility of increased skin photosensitivity and advising the adoption of preventive measures such as the use of broad-spectrum sun protection with a protection factor equal to or greater than 30 and the use of physical protection such as hat, sunglasses and protective clothing (Gouveia et al., 2016) (Nahhas, Oberlin, Braunberger, & Lim, 2018). It should also be noted that solar radiation is not the only one involved in photosensitivity. UV-emitting lights, found in solariums and beauty centers, may also be involved and should be avoided by patients.

Another strategy that, in some cases, can be implemented is the administration of the drug at night, although this is highly dependent on its pharmacokinetic properties (Blakely et al., 2019). In strict photoprotection settings, the patient may be at increased risk of vitamin D deficiency due to lack of sun exposure. Vitamin D counseling should be considered (Nahhas et al., 2018).

Patients are rarely aware of the potential risk of an adverse skin reaction and in their daily life they use medication, especially over-the-counter drugs, without informing and consulting their physician. Thus, as the pharmacist is often the patient's first line of contact, it is essential to educate and make the patient aware of photosensitivity and the possible associated risks (Zuba et al., 2016).

DISCUSSION

Drug-induced photosensitivity is a common and frequent problem worldwide. Activation of the chromophore by UV radiation induces a nonspecific inflammatory reaction (phototoxicity reaction) or a T-cell mediated immune reaction (photoallergy reaction). Many of the drugs involved in the reactions have the ability to cause both reactions, which does not facilitate the process of differentiation and diagnosis.

Phototoxicity presents as the most common clinical pattern erythema similar to sunburn. Photoallergy is more commonly associated with eczema and photoallergic contact dermatitis.

The photosensitizing properties of pharmacological therapies are, in large number, associated with their chemical structure. Drugs with polycyclic aromatic rings are more involved in the reactions. They can also be associated with cross-reactions between compounds with similar chemical structures.

The photosensitivity induced by ketoprofen is non-specific as it can induce both reactions. It can be justified by the production of ROS and cross reactions derived from the benzophenone compound. The photosensitivity to fenofibrate is also associated with this compound and with this, there must be a double attention in individuals who make both therapies together.

In the case of piroxicam, its photosensitizing properties are associated with sensitization to thimerosal, that is, individuals previously sensitized to thimerosal may develop photoallergy in the first contact with it, through a cross-reaction.

FQ that contain a halogen in the 8th position of their chemical structure are considered to have the greatest phototoxic potential. This is the case of lomefloxacin, sparfloxacin and clinafloxacin.

Voriconazole-induced phototoxicity is associated with its active metabolite: N-oxide. Retinoid-induced photosensitivity may be associated with voriconazole co-administration, as tretinoin is metabolized by CYP450 isoenzymes and voriconazole is an inhibitor of these enzymes.

Antihypertensive drugs and statins, being chronic therapies, require special attention because chronic exposure to photosensitizing drugs is associated with an increased risk of skin complications, such as skin cancer.

Unlike other drugs, vemurafenib induces a direct and immediate reaction during exposure to UV radiation. It presents as a feeling of heat and erythema with possible edema.

CONCLUSION

Drug induced phototoxicity and photoallergy are two types of photoreactions than can result from the exposure of the patient to a UV radiation, due to interaction with drugs. A large number of associations between drugs and photoreactions have been reported, both with systemic and topic formulations. Nevertheless, the level of evidence for most associations between oral drugs and phototoxicity has not been assessed. Vemurafenib, NSAID, fluoroquinolone, retinoids and tetracycline antibiotics seem to have the strongest level of evidence as inducers of phototoxicity and special care should be taken during treatments with those drugs, regarding exposition to the sun or other source of UV radiation.

As for future perspectives, DIP requires further investigation on the mechanisms involved and the associated risk, since severe reactions can limit the use of drugs and have consequences for the health of the population. It would be important to analyze the role of drug excipients in inducing photosensitivity. Likewise, it is of utmost importance to assess and improve the populations' literacy on DIP. A multidisciplinary team of healthcare professionals should be involved in the management and prevention of photoreactions, and the use of phototesting is also recommended.

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