Portuguese Journal of Dermatology and Venereology

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Fluoroquinolones as enhancers of photocarcinogenesis: Proposed pathomechanisms

O papel das fluoroquinolonas no mecanismo de fotocarcinogénese

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Abstract

Fluoroquinolones are photosensitizing drugs in humans, as they can enhance effects of ultraviolet A (UVA) radiation on the skin. UVA causes lesions both to deoxyribonucleic acid and other cellular organelles by Type I and Type II reactions (major and minor). The resulting photoproducts are highly reactive and can change the chemical composition of nucleotide bases, induce strand breaks and disrupt macromolecules and organelles. The cellular response can trigger apoptosis, causing a phototoxic skin reaction, recognized clinically as erythema, bullous or eczematous lesions, pseudoporphyria, onycholysis or subcorneal pustules. Moreover, cells with defects in oncogenes and/or tumor suppressor genes may be unable to promote apoptosis and thus give rise to a tumor cell. There has been growing evidence in the literature that photosensitizing drugs increase the photocarcinogenesis potential of UV radiation. In addition to being photocarcinogenic, UV radiation is immunosuppressive, which may explain why tumor cells multiply without control. The immunosuppression seems to be enhanced by fluoroquinolones. These drugs have proven to be photogenotoxic and photocarcinogenic *in vitro* and in animals. Clinical studies seem to suggest an increased risk of skin cancer in patients taking fluoroquinolones, with an even higher risk with longer courses of treatment. This article suggests a possible association between fluoroquinolones and skin cancer but also highlights a gap in the literature. Thus, it is important to increase preventive measures regarding sun exposure.

Keywords: Deoxyribonucleic acid/radiation effects. Deoxyribonucleic acid damage; dermatitis. Phototoxic. Fluoroquinolones. Radiation-sensitizing agents. Skin neoplasms/genetics.

Resumo

As fluoroquinolonas atuam como substâncias fotossensibilizantes, potenciando os efeitos da radiação UVA na pele. A radiação UVA desencadeia lesões tanto no ADN como nos restantes organelos celulares por reações de tipo I e tipo II (*major e minor*), cujos produtos de reação altamente reativos são capazes de alterar a composição química das bases de nucleótidos, induzir quebras da cadeia, oxidar macromoléculas e organelos. A reposta celular pode desencadear mecanismos de apoptose, provocando uma reação de fototoxicidade na pele, que pode ser reconhecida clinicamente como eritema, lesões bolhosas ou eczematosas, pseudoporfiria, onicólise ou pústulas subcorneas. Além disso, as células com lesões em oncogenes e/ou

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Received: 14-02-2022
Accepted: 23-02-2022
DOI: 10.24875/PJD.M22000006

Available online: 16-05-2022
Port J Dermatol and Venereol. 2022;80(1):33-41
www.portuguesejournalofdermatology.com

genes supressores tumorais podem não ser capazes de promover a apoptose e, desta forma, originar uma célula tumoral. Tem havido uma crescente evidência na literatura de que fármacos fotossensibilizantes aumentam o potencial fotocarcinogénico da radiação UV. Além de fotocarcinogénica, a radiação UV é imunossupressora, o que pode justificar que células tumorais proliferem sem controlo. O estado de imunossupressão parece ser também agravado pelas fluorquinolones. Estes fármacos provaram ser fotogenotóxicos e fotocarcinogénicos em estudos *in vitro* e em animais. Os estudos clínicos parecem sugerir um risco aumentado de aparecimento de cancro de pele em doentes a tomar fluoroquinolonas, havendo um aparente incremento do risco em tratamentos mais longos. O presente artigo conclui uma possível associação entre a toma de fluoroquinolonas e risco de cancro cutâneo, mas também evidencia uma lacuna de estudos na literatura. Desta forma, é importante reforçar as medidas preventivas face à exposição solar.

Palavras-chave: Ácido desoxirribonucleico/efeitos de radiação. Danos ao ácido desoxirribonucleico; dermatite. Fototóxico. Fluoroquinolonas. Agentes sensibilizadores de radiação. Neoplasias cutâneas/genética.

Introduction

Ultraviolet (UV) radiation is a potent and complete carcinogen. UVB is absorbed by the deoxyribonucleic acid (DNA) molecule, and consequently, photolesions are formed: cyclobutene pyrimidine dimers (CPDs) and pyrimidine (6-4) pyrimidone (6-4 PPs)[1]. On the other hand, DNA damage induced by ultraviolet A (UVA) depends on indirect mechanisms in which reactive oxygen species (ROS) are generated through photoactivation of endogenous photosensitizers such as porphyrins, tryptophan[2], or exogenous photosensitizers, including fluoroquinolones (FQ)[3]. There has been growing evidence in the literature that photosensitizing drugs increase the photocarcinogenesis potential of UV radiation[4-7] for instance diuretics (hydrochlorothiazide), non-steroidal anti-inflammatory drugs (naproxen), cardiovascular drugs, chlorpromazine, tetracyclines, and quinolones.

Quinolones are antimicrobials classified according to their action spectra. Nalidixic acid was the first quinolone antibiotic (first-generation). The second-generation quinolones are fluoroquinolones since they have a fluorine at position six and include ciprofloxacin, enoxacin, lomefloxacin, norfloxacin, and ofloxacin. The third-generation quinolones are levofloxacin, sparfloxacin and moxifloxacin and have more than one fluorine atom in its composition[8].

Nalidixic acid was the first quinolone used as an antibiotic, and in 1964, the first case of a photosensitivity reaction presenting as a pseudo-porphyria was described[9]. Since then, phototoxicity has been widely studied also with other quinolones, namely the fluorquinolones[10-16]. The clinical aspects favoring a possible phototoxic reaction include erythema, eczematous or bullous lesions, pseudo-porphyria, photo-onycholysis, and subcorneal pustules, although some occasional cases of photoallergy also occur[10]. In addition to phototoxicity, FQ has been investigated for their photocarcinogenesis potential[16-21].

The present review focuses on the accumulate evidence found for the photocarcinogenic potential of FQ in *in vitro* and animal studies, as well as clinical studies to elucidate if FQ are responsible for the appearance of skin tumors in individuals chronically exposed to these drugs.

Photocarcinogenesis

Direct UV-radiation damage

UVB radiation is directly absorbed by DNA and generates CPDs and 6-4 PPs in a 2:1 ratio. These photoproducts lead to mismatches during DNA replication[22]. Within CPDs, TC and CC dimers are the most mutagenic. TC → TT and CC → TT mutations are the ones most frequently found in the *p53* gene in UV-induced skin cancers[2]. The most important reaction is deamination, converting cytosine to uracil. For instance, TC CT and CC CPDs turn into TU UT and UU CPDs, respectively. During replication, the U residues in the codon lead to the incorporation of an adenosine base, which in the next replication pairs up with T, which results in the characteristic mutations of photocarcinogenesis, namely T → C at TC sites and the CC → TT mutation. Furthermore, 6-4 PPs undergo deamination, but only at the 5' DNA strand, with the 6-4 PPs TT being the most mutagenic[23]. In mammals, the most important mechanism for removing these errors is the nucleotide excision repair (NER)[24]. Individuals with xeroderma pigmentosum have defects in this repair system; thus, they are more prone to develop skin cancer at younger ages[25].

UVA radiation also causes DNA damage through oxygen-dependent reactions involving photosensitization. This process results in oxygen and nitrogen reactive species that lead to the formation of 8-oxo-7, 8-dihydroguanine (8-oxoGua) and single-strand breaks[23]. UVB is also capable of generating 8-oxoGua through the oxidation of the guanine base by the

•OH radical[26]. All three types of photoproducts (CPDs, 6-4 PPs, and 8-oxoGua) are premutagenic. Their carcinogenic potential depends not only on the type of photoproduct, but also on the nucleotide sequence into which they are inserted[24].

The most common skin cancers are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma (ordered from most common to least and from least to most aggressive). Depending on the tumor type, various signaling pathways may be affected. In BCC, *Patched* and *Smoothened* mutations influence aberrant activation of the *Sonic hedgehog* pathway, promoting cell proliferation and tumor growth. In the case of SCC, mutations in the *p53* gene (*TP53*), the epidermal growth factor receptor gene, *Rat sarcoma* (*RAS*), c-fyn proto-oncogenic proteins (FYN), and cyclin-dependent kinase inhibitor 2A (*CDKN2A*) are involved. Melanoma has different UV-induced mutations including those of *TP53* and *CDKN2A*[22].

The promotion of cell proliferation caused by UV-induced mutations is, among others, mediated by the mitogen-activated protein kinase pathway. The RAS protein represents one of three oncogenes involved in this pathway whose mutations can lead to continuous receptor-independent proliferation, promoting tumor growth. These mutations have been detected in melanoma *N-RAS* genes and are caused by sun exposure, since these genes have a large amount of pyrimidine sequences. The RAS protein is one of the inhibition transducing signals of the hepatocyte growth factor (MET) receptor, which may lead to the appearance of melanoma when overexpressed[22,27]. Both BCC and SCC exhibit specific mutations in the *TP53*, located at PDs, both CPDs and 6-4 PPs. These mutations are considered characteristic of the effect of UVB[27].

Inflammation also plays an important role in photocarcinogenesis. UV radiation induces cyclooxygenase-2 (COX-2) gene transcription. From arachidonic acid, COX-2 synthesizes prostaglandins (PG) that initiate the inflammatory process. UV radiation increases the amount of arachidonic acid while maintaining a continuous synthesis of PG in the skin, which contributes to the process of carcinogenesis and tumor progression[22]. COX-2 and PGE2 can be triggered by ROS, as well[28].

Damage by production of ROS

UVA radiation is barely absorbed by DNA, nonetheless, it is carcinogenic, as it indirectly causes DNA damage through photosensitizers[1]. A photosensitizer in a singlet excited state reacts directly with neighboring chemicals, causing injury to macromolecules and cellular organelles. However, in a triplet excited state, the photosensitizer is more stable and has a longer lifetime[29]. UVA radiation induces the formation of CPDs as the result of an energy transfer from the photosensitizer in a triplet excited state to the pyrimidine bases[30]. UVA radiation causes DNA damage through two mechanisms: (i) oxidation of substrate with loss of an electron (Type I mechanism) and/or (ii) production of ROS (Type II minor mechanism) or singlet oxygen ($^1O_2$) (type II major mechanism)[31].

Type I mechanism involves the transfer of an electron through the direct interaction of the excited photosensitizer with DNA, generating an intermediate radical. The initial step of this reaction does not require oxygen, but it can participate in subsequent reactions. This mechanism is dependent on the oxidation potential of the DNA base and the reduction potential of the photosensitizer. Of the four DNA bases, guanine has the lowest oxidation potential, therefore it is the most likely base to be oxidized. The Type II major mechanism involves the transfer of energy from an excited photosensitizer to an oxygen molecule (O_2) to produce singlet oxygen $^1O_2$, a potent oxidant with a long lifetime, which reacts with DNA, especially at guanine bases and leads to the formation of 8-oxoGua. The minor type II mechanism requires the formation of superoxide anion (O_2^-) through the transfer of an electron from the photosensitizer to the oxygen molecule, followed by dismutation into hydrogen peroxide (H_2O_2). Both O_2^- and H_2O_2 are not able to directly damage DNA. In the presence of metal ions, H_2O_2 can damage DNA by reacting with Fe(II) to form the free hydroxyl radical (·OH) in the so-called Fenton reaction. The ·OH radical injures DNA without any specificity to the nucleotide. In contrast to this radical, copper-oxygen complexes, formed in a reaction involving H_2O_2 and Cu(II), induces lesions at specific sites in DNA, namely at thymine and guanine residues[1,30,31].

In Type I mechanism, the lesion occurs specifically at 5'-G in the 5'-GG-3' sequence, while the Type II major mechanism acts on a guanine residue without specificity for consecutive guanines. 8-oxoGua is accounted for as the result of the guanines' damage and can lead to incorrect DNA replication, resulting in mutations, namely transversion G → T. These mutations in consecutive guanines present in *RAS* oncogenes, for example, GGT → TGT and GGC → TGC, are found in human skin cancers. These mutations are preceded by the formation of 8-oxoGua at 5'-G in the 5'-GG-3' sequence through the Type I reaction[1,30]. Table 1 summarizes alterations in DNA nucleotides caused by UV radiation.

Table 1. Lesions and mutations in the DNA caused by UV radiation

UVB	UVA Type I reaction	UVA major Type II reaction
G → 8-oxoGua (rare lesion)	5′-GG-3′ → 5′-8-oxoGuaG-3′	G → 8-oxoGua (Without specificity for consecutive guanines)
Normal DNA TT → TT 6-4 PPs	GGT → TGT GGC → TGC	G → T
TC CPDs → TT CPDs CC CPDs → TT CPDs		

UV: ultraviolet; CPDs: cyclobutane pyrimidine dimers; 6-4 PPs: pyrimidine-(6-4)-pyrimidone photoproducts; T: thymine; C: cytosine; 8-oxoGua: 8-hydroxyguanine.

Photoimmunosuppression

Despite the antigenic capacity of UV-induced skin tumors cells that might generate an immune response favoring tumor immunosurveillance, skin cancer has a high frequency in the population, especially those with higher sun exposure. Studies have shown that UV radiation induces local immunosuppression as it down-regulates or even inhibits the systemic immune response to antigens from mutated cells. Therefore, tumor cells proliferate without an immune response[32].

Since the studies of Margaret Kripke in 1970's, it is known that in mice highly antigenic UV-induced UV-induced tumors transplanted into normal non-UV irradiated mice were completely rejected, unless they were transplanted into an UV-irradiated area (local photoimmunosuppression) or to a non-irradiated area in mice exposed in other areas to high UV doses (systemic photoimmunosuppression)[33]. Although mechanisms of photoimmunusuppression are not completely understood, UV-induced DNA damage has shown to reduce the number of Langerhans cells and other dendritic cells in the skin. Moreover, their capacity to effectively present antigens to T cells involved in the anti-tumor response is abrogated, namely through the production of PGE_2 and immunoregulatory cytokines (IL-10, IL-4)[34].

FQ and photocarcinogenesis

In vitro studies

FQ has been shown to be photogenotoxic *in vitro*: Reavy et al.[18] tested rat fibroblast cells and observed that UVA-irradiated FQ penetrated the fibroblasts and led to DNA single breaks. This could be explained by the production of[1] O_2 and O_2^- when FQ are irradiated by UVA[35]. Marrot and Agapakis-Causse[36] used both supercoiled plasmids DNA and diploid chains of yeasts *Saccharomyces cerevisae* under UVA radiation and were able to conclude that the potential for phototoxicity involved several factors: ROS production, photoproduction of toxic subproducts, direct interactions with DNA with possible impact on replication and/or transcription.

The most photomutagenic and photocarcinogenic FQ *in vitro* are lomefloxacin and fleroxacin since both have an extra fluorine atom at position 8[37]. However, FQ that only have the fluorine at position 6 are also capable of causing considerable damage (Fig. 1). Sauvaigo et al.[38] worked with calf thymus DNA under UVA and observed that norfloxacin and ofloxacin were able to induce single breaks. The loss of the fluorine is associated with the production of a highly reactive carbene at position 8 in the case of lomefloxacin and at position 6 in the case of enofloxacin, norfloxacin and ofloxacin. However, the rate at which the FQ loose fluorine is much faster in lomefloxacin than in the others. The aryl cations resulting from the subsequent reactions are highly reactive and may be involved in the degradation of nearby biomolecules[38]. The loss of the fluorine seems to be the main process involved in the phototoxic effect of FQ. However, this photodegradation process is not significant in ciprofloxacin and moxifloxacin. For these FQ, irradiation under an aerobic environment gives rise to N-demethylation of the piperazinyl ring thgrough photoionization from a single state and formation of hydrated electrons, as well as[1] O_2 generation from triplet excited state drug[39].

Under UVA radiation, FQ can act as a chromophore as they absorb sufficient energy, reaching a triplet excited state. In this process, an energy transfer occurs and CPDs are formed[31]. Lhiaubet-Vallet et al.[40] used supercoiled circular DNA under UVA+FQ and observed that norfloxacin and enoxacin were able to generate CPDs. Hiraku and Kawanishi[41] worked with lomefloxacin and DNA fragments containing the human *c-Há-ras-1* proto-oncogene and the human tumor suppressor gene *TP53* under UVA. They concluded that lemofloxacin can damage every single guanine residue and enhance the formation of 8-oxoGua. These lesions can subsequently lead to aberrant DNA replication and mutations[41].

Since oxidative stress is implicated in cellular and molecular damage, cells possess a complex antioxidant system, which includes the conversion of ROS to harmless compounds by antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione[29]. The photosensitization of FQ generate ROS[18,35] that

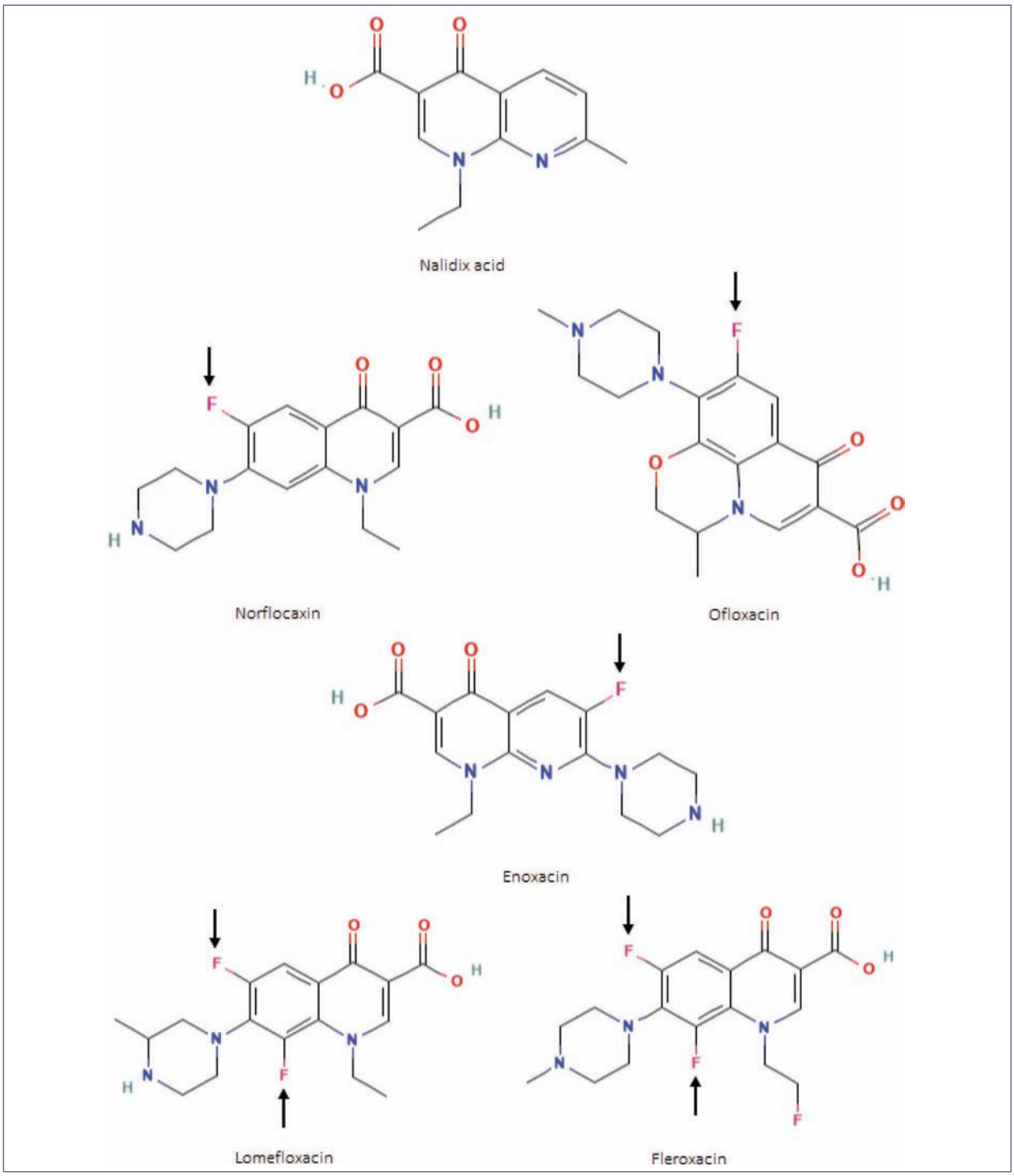

Figure 1. Structural formula of some quinolones. Fluor atoms that suffer the action of UV radiation are marked by an arrow.

can disturb the complex antioxidant system. Kowalska et al.[29] used human epidermal melanocyte cells exposed to UVA and moxifloxacin and observed a reduction in SOD activity compared to control, a decreased in mitochondrial SOD2 mRNA levels and a reduction in catalase activity. In addition to scavengers, melanin also neutralizes ROS and thus exerts a protective effect on the cell. However, FQ can bind to melanin and form FQ-melanin complexes. These complexes may lead to the accumulation of the FQ in the cell and increase its toxicity[29].

An erratic NER is often associated with photosensitivity and a high incidence of skin cancer. This system repairs pre-mutagenic DNA by removing CPDs

and 6-4 PPs lesions. Human replication protein A is one of the essential components of NER and is extremely sensitive to oxidation. FQ can generate oxidative stress in the cell, which inevitably leads to oxidation of human replication protein A. Oxidized protein is associated with decreased repair capacity of NER. The vulnerability of NER may lead to a connection between skin photosensitivity and an increased risk of skin cancer[42].

Moreover, FQ can enhance photoimmunosuppression contributing to a lack of response against mutated cells, which therefore multiply under no immune control. Singh et al.[43] worked with pefloxacin on a human keratinocyte cell line (HaCaT) exposed to UVA radiation and observed a promotion of immune suppression with non-toxic doses in peritoneal macrophages through a significant reduction of interleukin-1, interleukin-6, and tumor necrosis factor-alfa. Sun et al.[44] demonstrated that pefloxacin and ciprofloxacin further decreased the number of Langerhans cells locally, therefore abrogating their function in the presentation of antigens to the cells of the immune system.

Animal studies

In an initial and short exposure to significant levels of UV radiation, the skin reaction includes apoptosis of keratinocytes and inflammation, followed by epidermal hyperplasia. In UV exposed animals, this stage regresses if irradiation is discontinued. If exposure is prolonged, epidermal hyperplasia is observed before the onset of neoplasia. Hyperplasia combined with cytological dysplasia, classified in humans as solar keratosis, is a common lesion due to repeated chronic UV exposure[45]. Mäkinen et al.[45] irradiated with UVA lightly pigmented Skh-1 mice taking FQ and detected SC lesions with severe changes in nucleus and cell size and occasionally observed disorganization in epithelial cell layers which together could be considered as signs of carcinoma *in situ*. Furthermore, the authors observed lesions in these mice such as papillomas, keratoacanthomas, solar keratosis, and SCC, a definitive marker of carcinogenesis from both chemicals and UV radiation. Furthermore, other studies showed FQ were photocarcinogenic in mice: animals exposed to fleroxacin+UVA, ciprofloxacin+UVA and ofloxacin+UVA exhibited an increase in benign tumors when compared to animals exposed to UVA alone; and in rats exposed to lomefloxacin+UVA both the number of benign and malignant tumors was higher, even higher that psoralens, and these tumors occurred quite early during the experiment[45]. Klecaket al.[17] performed studies in lightly pigmented Skh-1 mice, which were exposed to various FQ and UVA and could observed the appearance of the same types of benign tumors (papillomas, keratoacanthomas) and malignant (SCC) when exposed to lomefloxacin. Further studies[19,46] reinforce the evidence that FQ can induce both benign and malignant tumors *in vivo*.

The absence of a functional NER is associated with an increase in the photocarcinogenic potential of FQ since there is no longer a repair of DNA lesions. If these lesions occur in strategic places such as tumor suppressor genes or oncogenes, the appearance of a tumor cell may occur. Itoh et al.[47] used mice with a defect in PD repair, homozygous for the absence of the *XPA* gene that encodes a NER protein and observed a large number of SCC in mice exposed to lomefloxacin and UVA.

Clinical studies

Photosensitizing drugs have been extensively studied, and there has been growing evidence that these drugs increase the photocarcinogenesis risk[48]. Hydrochlorothiazide is one of the drugs in which a correlation, even if modest, has been established between its use and the onset of nonmelanoma skin cancer (NMSC: SCC and BCC)[49]. For this reason, Infarmed, in conjunction with the European Medicines Agency, issued a communication addressed to health professionals, advising to strengthen sun protection measures and rethink the use of the hydrochlorothiazide in patients with a history of skin cancer[50]. In recent years, several studies have evaluated the association between FQ therapy and the risk of skin cancer. Table 2 presents some of their methodological elements and their main results.

Studies in the United States seem to demonstrate an association between therapy with photosensitizing drugs and the risk of NMSC. In 2007, Karagas et al.[7] observed a significant association with a probability (odds ratio [OR]) of 1.5 (95% confidence interval [CI], 1.0-2.4) for BCC and a rate of 1.8 (95% CI, 1.1-3.2) for SCC. There was also a clear increase in risk with a treatment longer than 1 year (BCC: OR 1.9; 95% CI, 1.1-3.3 and SCC: OR 2.3; 95% CI, 1.1-4.5). In 2013, Robinson et al.[5] studied a population consisting of individuals diagnosed with NMSC. Subjects who were on an antimicrobial treatment, including FQ, had an

Table 2. Studies assessing the association of FQ therapy and skin cancer risk: main results

Reference	Type of study	Study population	BCC	SCC	Melanoma
Karagas et al.[7]	Case-control	582 BCC 281 SCC 532 controls	Associated photosensitizing drugs OR 1.5 IC 95%, 1.0-2.4	Associated photosensitizing drugs OR 1.8 IC 95%, 1.1-3.2	Not evaluated
Robinson et al.[5]	Case-control	1,637 BCC 1,605 SCC 1,952 controls	Associated antimicrobials OR 1.9 95% CI 1.3-2.8 Associated antimicrobials (>1 y) OR 1.9 95% CI 1.0-3.7	Associated antimicrobials OR 1.4 IC 95%, 0.9-2.1	Not evaluated
Siiskonen et al.[51]	Case-control	1,318 melanoma 6,786 controls	Not evaluated	Not evaluated	Associated quinolones R_{adj} 1.33 95% IC 1.01-1.76
Kaae et al.[6]		4,761,749 individuals	Associated ciprofloxacin IRR 1.2; 95% IC 1.1-1.2 Associated levofloxacin IRR 1.5; 95% IC 1.1-2.1 Associated levofloxacin (long treatment course) IRR 1.7 95% IC 0.7-3.9	Associated ciprofloxacin IRR 1.3 95% IC 1.2-1.4 Associated levofloxacin IRR 1.0 95% IC 0.4-2.3 Associated levofloxacin (long treatment course) IRR 1.5 95% IC 0.1-29	Associated levofloxacin (long treatment course) IRR 1.5 95% IC 0.03-84

BCC: basal cell carcinoma; SCC: squamous cell carcinoma; OR: odds ratio; OR_{adj}: adjusted odds ratio; IRR: incident ratio rate.

increased risk for SCC (OR 1.4; 95% CI, 0.9-2.1) and for BCC (OR 1.9; 95% CI 1.3-2.8). The risk was considerably higher with a treatment longer than 1 year for BCC (OR 1.9; 95% CI 1.0-3.7)[5].

In the Netherlands, a study was conduct with individuals histologically diagnosed with melanoma. Taking quinolones appears to be related to an increased risk of developing melanoma (adjusted OR [OR_{adj}] 1.33; 95% CI 1.01-1.76), even when used for a short period of time corresponding to standard treatment[51].

In 2010, a cohort study was designed in Denmark to infer the association of photosensitizing drugs and the risk of onset of skin cancer (SCC, BCC and melanoma). The study was divided into long and short treatment drugs (including ciprofloxacin and levofloxacin). There was an increased risk of skin cancer of more than 20% in patients on short treatment drugs compared to non-users. The FQ short treatment was associated with an increased risk of BCC (ciprofloxacin incident ratio rate [IRR] 1.2; 95% CI 1.1-1.2 and levofloxacin IRR 1.5; 95% CI 1.1-2.1) and SCC (ciprofloxacin IRR 1.3; 95% CI 1.2-1.4 and levofloxacin IRR 1.0; 95% CI 0.4-2.3). The short treatment was extended in some subjects, whose risk for developing a tumor was significantly increased, especially for levofloxacin: BCC (IRR 1.7; 95% CI 0.7-3.9); melanoma (IRR 1.5; 95% CI 0.03-84) and SCC (IRR 1.5; 95% CI 0.1-29)[6].

Although clinical studies can provide some evidence that there is a significant role in photosensitization, and subsequently, the appearance of tumors, these drugs are still widely prescribed, given that most are for short treatments. However, there is a range of patients who require long courses of treatment, notably in indwelling patients for prophylaxis of urinary tract infections or in the treatment of leprosy and tuberculosis. There is a clear lack of evidence, due to a lack of studies, on the effect of prolonged treatment with FQ. On the other hand, there is a clear evidence that hydroclothiazide, a long treatment photosensitizing drug, is associated with the appearance of non-melanoma skin tumors[49]. For this reason, its replacement has been recommended[50]. This increasing risk of photocarcinogenisis in patients exposed to photosensitizing drugs may be further enhanced in a subpopulation of patients with chronic pharmacologic-induced immunossuppression (e.g., solid organ transplanted patients), as it has been shown that these patients have an increased risk of UV-induced skin tumors[52] (eef Pinho et al.) and the use of photosensitizers is this population, namely voriconazole, is significantly associated with rapidly growing SCC and even melanoma.

Therefore, clinical studies with the main objective of investigating the photosensitizing effects in patients taking long-treatment FQ, as well as other photosensitizers, are highly needed.

Prevention

Given the evidence in the literature, although not completely clear, it is always good clinical practice to advise patients. Aiming for the prevention of skin cancer, some recommendations include avoidance of exposure to sunlight between 11 a.m. and 4 p.m., use of a hat and appropriate clothing such as cotton clothing with a tighter knit or higher density, use of sunscreen with protection index equal or superior to 50 and education in recognizing the alarm signs of pigmented or keratotic lesions or non-healing skin ulcers. The physician may also opt for a more preventive action by advising drug administration at the end of the day to reduce the circulating dose during sunlight hours.

Conclusion

FQ can act as photosensitizing drugs under UVA radiation and cause DNA damage. If the lesions take place in oncogenes and/or tumor suppressors and are not repaired, it can trigger the appearance of a tumor cell. The immunosuppression caused by UV radiation can be enhanced by FQ, worsening the picture of uncontrolled cancer cell proliferation. FQ has been shown to be photogenotoxic and photocarcinogenic both *in vitro* and in animals. Clinical studies seem to suggest an increased risk of skin cancer also in patients taking FQ. This article reinforces the association between taking FQ and the risk of skin cancer, but it also highlights the shortage of studies on the subject. More studies need to be proposed with a robust methodological design that control potential modifiers, such as sun exposure, phototype, and treatment length to identify the true magnitude of the relationship between FQ therapy and skin cancer.

What does this study add?

The authors call the attention to the capacity of fluorquinolones to enhance UV-induced skin carcinogenesis in animal and in vitro studies, with possible relevant effect in humans exposed to these antibiotics.

Author's contributions

Margarida Gonçalo raised the question, collaborated in the review, organized the presentation of the data, and corrected the final version of the manuscript. Ricardo Lopes performed the bibliographic review, analyzed information, drafted the manuscript, and approved the final version.

Funding

This work has not received any contribution grant or scholarship.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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