Mechanisms of photosensitization induced by drugs: A general survey

Mecanismos de fotosensibilización inducida por fármacos: Una visión general

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ABSTRACT

This paper presents a general survey of the mechanisms involved in drug phototoxicity. Moreover, a list of 174 currently used clinical drugs inducing photosensitization is provided in addition to some others from which phototoxic effects are suspected. Likewise, some aspects related to the mechanisms involved in the phototoxicity of fluoroquinolones and non steroidal-antiinflammatory drugs have been reviewed. Finally, a possible role of the arenediazonium ions as photosensitisers is discussed.
KEY WORDS: Phototoxicity. Drugs. Mechanisms. Photosensitization. Fluoroquinolones. Non-Steroidal Antiinflammatory drugs. Arenediazonium ions

RESUMEN

En el presente trabajo se hace ofrece una visión general los mecanismos relacionados con la fototoxicidad de sustancias farmacológicamente activas. Además se ha confeccionado una lista de 174 compuestos utilizados en la actualidad en la práctica clínica y de los que se existe pruebas de su actividad fototóxica. Conjuntamente se ofrece otra relación con sustancias cuyos efectos fototóxicos se sospechan. Asimismo, se revisan algunos aspectos relacionados con los mecanismos de fotoxicidad de fluoroquinolonas y antiinflamatorios no esteroídicos. Por último, se discute la posible actividad fotosensibilizadora de los iones arenodiazónicos
PALABRAS CLAVES: Fototoxicidad. Fármacos. Mecanismos. Fotosensibilización. Fluorquinolonas. Antiinflamatorios no esteroídicos. Iones arenodiazónicos

INTRODUCTION

The treatment of deseases requires occasionally the use of either systemic or topical medication during certain period of time. Frequently the treatment coincides with exposures to electromagnetic radiations coming from different types of sources (sunlight in works made outdoor, or in vacational seasons, intense artificial radiations used in specific works, etc.). That coincidence may lead to the appearance of unexpected effects varying from just a simple rash to severe cutaneous affectations. Moreover other problems may also arise from the damage of internal organs following the drug-radiation interaction.

Interaction between the electromagnetic radiation and the matter encompasses a great number of events among which photophysical and photochemical processes can be included. Those reactions which involve UV/Vis radiation and biological systems are particularly interesting because of their wide field of applications

(environmental, energetic, biological...). One of the biological applications is the *photosensitization* phenomena. Photosensitization reactions is a continously growing area of research which deals with the desirable and undesirable processes induced in biological systems by the absorption of UV/Vis radiation (Beijersbergen van Henegouwen, 1997).

In general, photosensitization is an abnormally high reactivity of a biological substrate to artificial sources or natural sunlight providing, in principle, ineffective doses of UVA, UVB and Vis radiations. Photosensitization requires the presence in the biological medium of certain substances known as *photosensitisers* which induce the changes in the biological substrate after absorbing appropriate radiation (Beijersbergen van Henegouwen, 1981) (Spikes, 1989) (Miranda, 1992) (Spielmann et al, 1994). The photosensitisers structural requirements to induce phototoxicity are related with the ability for absorbing those radiation wavelengths which present a better skin penetration (above 310 nm) favouring the subsequent photochemical decomposition to form stable photoproducts, free radicals and/or singlet oxygen (Condorelli et al., 1996a). It is possible to find photosensitisers in the cellular content (e.g. flavins and porphyrins), in foods, cosmetics, some plants or their juices, industrial chemicals (dyes, coal tar, derivatives chlorinated hydrocarbons..) and drugs. In addition to so broad distribution, the exogenous photosensitisers may enter into the body through different ways as well: ingestion, inhalation, injection or direct contact with the skin or mucouses.

With regard to drugs, photosensitization reactions can be used in a therapeutic approach; i.e. photodynamic therapy (Henderson and Dougherty., 1992) (Dougherty and Marcus, 1992) (Szeimies et al., 1996), blood purification (Margolis-Nunno et al., 1996), inactivation of viruses (Sieber et al., 1992); or can appear as an adverse side-reaction. Biological targets for photosensitization are cell membranes, cytoplasme organelles and the nucleus .(Epe, 1993) originating minor effects such as cutaneous reactions: erythema, pruritus, urticaria and rash or severe effects such as genetic mutations, melanoma, etc. which not always concern the light-exposed areas but may reach internal organs as well (Beijersbergen van Henegouwen, 1981) (Epstein, 1989). The symptoms following noxious photosensitization reactions appear immediately after the skin exposure and they will vary depending on the amount of radiation absorbed, type and amount of photosensitiser, skin type, and age and sex of the person exposed. It is worth noting that photosensitivity may occur in every person, usually presents dose-dependence and may not happen the first time the drug is taken. In that case the reaction, less common than phototoxicity, is known as *photoallergy* and is mediated by the binding to skin protein (Pendlington et al., 1990) (Lovell, 1993) (Castell et al., 1998) (Miranda et al., 1999). Moreover, a delayed phototoxic effect can also appear as a consequence of a reservoir of sensitiser or its metabolites which act even several days after the drug is not detectable in plasma.

The importance of the photosensitization processes can be easily understood taking into account the increasing number of reports dealing with phototoxic effects induced by new pharmaceuticals which may be explained on the basis of the different biological effects induced by the photoproducts in relation to their parents molecules. Photophysical and photochemical studies, including exam of excitation and emision properties, identification of reaction intermediates, isolation of photoproducts, analysis of interaction with biological substrates, are often an adequate approach to analyze the mechanisms through phototoxic effects can be produced. In the present article a brief overview is made regarding the mechanisms of photoxicity induced by drugs

PHOTOSENSITIZATION MECHANISMS

Several authors (Foote, 1976, 1991), (Spikes, 1989), (Vargas et al., 1996) (Beijersbergen van Henegouwen, 1997) (Miranda, 1992, 1997) (Moore, 1998) reviewed chemical, medicinal and biological aspects of photosensitization reactions. The reaction starts with the radiation absorption by the photosensitiser which becomes electronically excited species. Usually the multiplicity of the excited state is one, so that the corresponding excited stated is named singlet

state. The lifetime of the exited singlet state is very short (10^{-10}-10^{-9} s). The monomolecular deactivation of the excited electronic states may occur by a radiative (fluorescence) or non-radiative processes (internal conversion or intersystem crossing). Intersystem crossing implies a change in multiplicity in a such way that the excited molecule is found in a so-called excited triplet state which has a much longer lifetime (10^{-6}-10^{-3} s). Many photosensitization reactions proceed through a triplet state. So, a favoured intersystem crossing pathway must be expected for effective photosensitisers. Apart from the monomolecular pathway of deactivation for the excited photosensitiser (fluorescence, phosphorescence emission or non radiative deactivation), the fate of the photosensitisers in the excited state may be very different depending on the solvent, photosensitiser concentration, energy absorbed by the photosensitiser, type of substrate, proximity of substrate and photosensitiser, aerobic or anaerobic conditions, pH....

Four pathways are usually considered available for the excited photosensitisers (*Ph**) to exert phototoxic effects on some target in the biological substrate. First of all, an **energy transfer** [1] from excited triplet photosensitizer to the oxygen could produce excited singlet oxygen which might, in turn, participate in a lipid- and protein-membrane oxidation or induce a DNA damage.

$$Ph^* + O_2 \rightarrow Ph + {}^1O_2 \quad \Rightarrow \quad {}^1O_2 + target \qquad [1]$$

Second, an **electron or hydrogen transfer** could lead to the formation of free-radical species producing a direct attack on the biomolecules [2a] or in the presence of oxygen, to evolve towards secondary free radicals such as peroxyl radicals [2b] or the very reactive hydroxyl radical a known intermediate in the oxidative damage of DNA and other biomolecules. This latter pathway corresponds to sucesive reactions which involve the appearance of superoxide anion radical, its dismutation to form hydrogen peroxide followed with the hydrogen peroxide reduction to form hydroxyl radical. Generation of the radical takes place involving either the photosensitiser or the target biomolecule. These steps are outlined below [2c].

$$Ph^* \xrightarrow{electron\ or\ hydrogen\ transfer} Ph\bullet \quad \Rightarrow \quad Ph\bullet + target \qquad [2a]$$

$$Ph\bullet + O_2 \rightarrow PhO_2\bullet \quad \Rightarrow \quad PhO_2\bullet + target \qquad [2b]$$

$$Ph\bullet + O_2 \rightarrow Ph^+\bullet + O_2^{-\bullet} \quad \Rightarrow \quad O_2^{-\bullet} \rightarrow H_2O_2 \rightarrow OH\bullet \quad \Rightarrow \quad OH\bullet + target \qquad [2c]$$

Usually the direct radical mediated-reactions are called Type I reactions whereas singlet oxygen–mediated reactions are considered Type II (Foote, 1991). Frequently Type I and Type II reactions occur simultaneously and it is difficult to separate the effects corresponding to each Type. However, an experimental procedure has been reported to facilitate the study of pure radical effects (Aveline et al., 1998)

Many photosensitization reactions may be explained on the basis of the mechanism Type I or Type II, but are also possible additional pathways. Thus, a **covalent photobinding** [3] between photosensitiser and one particular macromolecule could take place inducing cell damage as well.

$$Ph^* + target \rightarrow Ph - target \qquad [3]$$

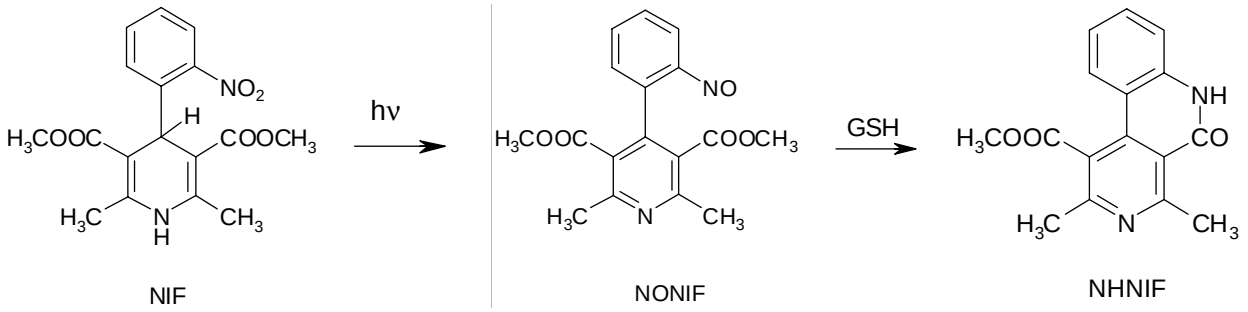
Finally, the photosensitiser could undergo a **decomposition** (probably via homolytic process) [4a-4b] so that the resulting photoproducts can act either as toxins or as new photosensitisers

$$Ph^* + (reductant\ or\ oxidant) \rightarrow Ph\bullet \rightarrow Photoproducts \quad \Rightarrow$$

$$Photoproducts + target \qquad [4a]$$

$$Photoproducts + h\nu \rightarrow Photoproducts^* \quad \Rightarrow \quad Photoproducts^* + target \qquad [4b]$$

An illustrative example for these latter pathways may be found in the study of the reactivity of nifedipine [NIF] a nitroaromatic molecule used in the treatment of myocardial ischemia and hypertension (De Vries et al., 1995, 1998). UV and visible radiations transforms NIF into its nitroso derivative [NONIF] in the absence of glutathione. Moreover, NIF irradiated with UV and visible light in the presence of glutathione originates the lactam [NHNIF] acting NONIF as an intermediate according to the following scheme.



NIF NONIF NHNIF

In vivo, after intravenous administration, NHNIF is rapidly (< 2 h.) cleared from the blood of rats and is excreted almost quantitatively via the bile, but in the HPLC exam of extracts of bile after the administration of NONIF or NIF (followed by UVA-exposure of the rat) less than 5% of initial concentration inoculed was detected as NHNIF plus a photoproduct derived from NHNIF. In principle, these results indicated that photoproduct can affect internal organs in the body. Besides, the results also suggested that, unlike NHNIF, a possible interaction with biomacromolecules could be expected for NONIF or NIF (in rat exposed to UVA radiation).

In addition, NIF, NONIF and NHNIF can be recovered quantitatively by one extraction with chloroform from aqueous solutions so that a similar lipophilicity is expected for all of them. Therefore no difference in capacity to complex protein present in the bovine serum albumine should be expected. However, samples of bovine serum albumine incubated with either NIF, NONIF and NHNIF in the dark or irradiated by UVA, analyzed by HPLC after extracting with chloroform showed recoveries near to 100% for NHNIF. At the contrary recoveries about 43-45% were obtained from the samples of bovine serum albumine incubated with either NIF and irradiated with UVA light or NONIF in the dark. These results agree well with the formation of an irreversible binding to biomacromolecules of NIF and its primary photoproduct NONIF. In this way, side effects of nitroaromatic nifedipine could in part be attributed to photoactivation of NIF which may be in competition with the enzymatic reduction of the nitro group.

DRUGS AS PHOTOSENSITISERS

In Table I is shown a non-exhaustive collection of phototoxic drugs pertaining to different therapeutic classes, i.e.; Antibiotics, Anti-diabetic drugs, Antihistamines, Cardiovascular drugs, Diuretics, Non-steroidal anti-inflammatory drugs (NSAIDs), Psychiatric drugs and others. The collected drugs appear in the literature as phototoxic either *in vivo* or *in vitro*. No consideration about its phototoxic potency has been made therefore potent phototoxic drugs are presented in Table I together with others inducing low phototoxic effects or, being potentially phototoxic, are currently under investigation. Photodynamic therapy (PDT) and PUVA-therapy photosensitisers have not been included otherwise they have an additional therapeutic use. The bibliographic sources used appear in the bottom of the Table I. In Table II appears some drugs for which phototoxic effects are suspected or exist, at least, one report claiming such phototoxic effects

TABLE I

Drug name	Therapeutic use[a]	Drug name	Therapeutic use[a]
Acetazolamide	Diuretic	Isoniazid	Antibacterial
Acetohexamide	Antidiabetic	Isothipendyl	Antihistaminic
Afloqualone	Muscular relaxant	Isotretinoin	Anti-acne
Alimezine	Neuroleptic	Ketoprofen	Anti-inflammatory
Alprazolam	Tranquilizer	Levofloxacin	Antibiotic
Amiloride	Diuretic	Levomepromazine	Neuroleptic
Amiodarone	Coronary vasodilator	Lomefloxacin	Antibiotic
Amitriptyline	Antidepressant	Loxapine	Tranquilizer
Amobarbital	Hipnotic	Maprotiline	Antidepressant
Amodiaquine	Antimalarial	Mefloquine	Antimalarial
Amoxapine	Antidepressant	Mequitazine	Antihistaminic
Bendroflumethiazide	Diuretic	Methazolamide	Diuretic
Benzthiazide	Diuretic	Methdilazine	Antipruritic
Benzydamide	Anti-inflammatory	Methotrexate	Antineoplastic
Bithionol	Anti-infective	Methiclothiazide	Diuretic
Bromochlorosalicylanilide	Antifungal	Methyldopa	Antihypertensive
Buclosamide	Antifungal	Metolazone	Diuretic
Captopril	Antyhypertensive	Minocycline	Antibacterial
Carbamazepine	Analgesic	Nabumetone	Anti-inflammatory
Carbutamide	Antidiabetic	Nalidixic acid	Antibacterial
Carprofen	Anti-inflammatory	Naproxen	Anti-inflammatory
Chlordiazepoxide	Tranquilizer	Nifedipine	Hypotensor
Chloroquine	Antimalarial	Norfloxacin	Antibiotic
Chlorothiazide	Diuretic	Nortriptyline	Antidepressant
Chlorpromazine	Tranquilizer	Ofloxacin	Antibiotic
Chlorpropamide	Antidiabetic	Orbifloxacin	Antibiotic
Chlorprothixene	Neuroleptic	Oxomemazine	Antihistaminic
Chlortetracycline	Antibacterial	Oxytetracycline	Antibacterial
Chlorthalidone	Diuretic	Paroxetine	Antipsycotic
Ciprofloxacin	Antibiotic	Pentobarbital	Hypnotic
Clinafoxacin	Antibiotic	Perazine	Neuroleptic
Clofazimine	Antibacterial	Perfloxacin	Antibiotic
Clofibrate	Antilipidemic	Periciazine	Antipsycotic
Clomipramine	Antidepressant	Perphenazine	Antipsycotic
Clozapine	Sedative	Phenothiazine	Antipsychotic
Dacarbazine	Antineoplastic	Phenylbutazone	Anti-inflammatory
Dantrolene	Muscle relaxant	Phenytoin	Anticonvulsant
Dapsone	Antibacterial	Piroxicam	Anti-inflammatory
Demeclocycline	Antibacterial	Polythiazide	Diuretic
Demethylchlorotetracycline	Antibacterial	Prochlorperazine	Anti-emetic
Desipramine	Antidepressant	Promazine	Tranquilizer
Diclofenac	Anti-inflammatory	Promethazine	Antihistaminic

Drug name	Therapeutic use[a]	Drug name	Therapeutic use[a]
Diflunisal	Anti-inflammatory.	Propiomazine	Antihistaminic
Diltiazem	Vasodilator	Prothipendyl	Neuroleptic
Dimethothiazine	Antihistaminic	Protriptyline	Antidepressant
Diphenhydramide	Antihistaminic	Pyrazinamide	Antibacterial
Dothiepin	Antidepressant	Quinacrine	Antimalarial
Doxepin	Antidepressant	Quinine	Antimalarial
Doxycycline	Antibacterial	Quinidine	Antiarrhythmic
Enalapril	Hypotensor	Risperidone	Anxiolytic
Enoxacin	Antibiotic	Rufloxacin	Antibiotic
Etretinate	Treatm.Psoriasis	Secobarbital	Hynotic
Felbamate	Antiepileptic	Sertraline	Antipsycotic
Felodipine	Hypotensor	Silver sufadiazine	Antibacterial
Fenofibrate	Antilipidemic	Sitafloxacin	Antibiotic
Fenticlor	Fungicide	Sparfloxacin	Antibiotic
Flecainide	Antiarrhythmic	Sulfamethoxazole	Antibacterial
Fleroxacin	Antibiotic	Sulfanylamide	Antibacterial
Floxuridine	Antineoplastic	Sulfasalazine	Antibacterial
Fluorouracil	Antineoplastic	Sulfisoxazole	Antibacterial
Flutamide	Antineoplastic	Suprofen	Anti-inflammatory
Fluoxetine	Antidepressant	Terfenadine	Antihistaminic
Fluphenazine	Antipsychotic	Tetrachlorosalicylanilide	Germicide
Furosemide	Diuretic	Tetracycline	Antibacterial
Gliblormuride	Antidiabetic	Thiazide	Diuretic
Gliclazide	Antidiabetic	Thiazimanium	Antihistaminic
Glimepiride	Antidiabetic	Thiethylperazine	Antihistaminic
Glipizide	Antidiabetic	Thioproperazine	Neuroleptic
Gliquidone	Antidiabetic	Thiopropazate	Antihistaminic
Glisentide	Antidiabetic	Thioridazine	Antipsychotic
Glisolamide	Antidiabetic	Thiothixene	Antipsychotic
Glisoxepide	Antidiabetic	Tiaprofenic acid	Anti-inflammatory
Glyburide	Antidiabetic	Tolazamide	Antidiabetic
Glycopyramide	Antidiabetic	Tolbutamide	Antidiabetic
Glycyclamide	Antidiabetic	Tolmetin	Anti-inflammatory
Grepafloxacin	Antibiotic	Trazodone	Antidepressant
Griseofulvin	Antifungal antibiotic	Tretinoin	Anti-acne
Haloperidol	Antidyskinetic	Triamterene	Diuretic
Hexachlorophene	Germicide	Trichlormethiazide	Diuretic
Hydralazine	Vasodilator	Triclosan	Germicide
Hydrochlorothiazide	Diuretic	Trifluoperazine	Antipsychotic
Hydroflumethiazide	Antihypertensive	Trifluprornazine	Antipsychotic
Hydroxychloroquine	Antimalarial	Trimeprazine	Antipruritic
Hydroxyethylpromethazine	Antihistaminic	Trimethoprim	Antibacterial

Drug name	Therapeutic use[a]	Drug name	Therapeutic use[a]
Imipramine	Antidepressant	Tripelennamine	Antihistaminic
Indapamide	Diuretic	Trovafloxacin	Antibiotic
Interferon beta	Antineoplastic	Valproic acid	Anticonvulsant
		Vinblastine	Antineoplastic

Data from Heid et al., 1977; Ljunggren et al., 1978, 1984, 1985a, 1985b; Przybilla et al. 1987a, 187b; Mozzanica et al., 1990; Nedorost et al., 1989; Hölzle et al., 1991; Kurimayi et al., 1992; Vargas et al; 1993; Kang et al., 1993; Tokura et al., 1994; Spielmann et al., 1994; Ishikana et al., 1994; Gould et al., 1995; Nabeya et al., 1995 Ferguson, 1995; Becker et al., 1996; Leroy et al., 1996; Condorelli et al., 1996a, 1996b, 1999; Eberlein-König, et al. 1997; Moore et al., 1998; Sortino et al., 1998; Spikes, 1998; Pazzagli et al., 1998; Ellis, 1998; Vilaplana et al., 1998; Ball et al., 1999; Snyder et al., 1999

[a] Therapeutic use taken from The Merck Index, 1983 and Martindale, 1996

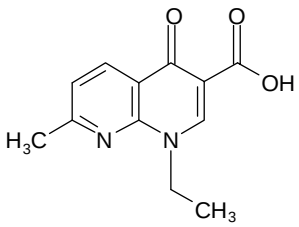
TABLE II

Drug name	Therapeutic use[a]	Drug name	Therapeutic use[a]
Amantadine	Antiviral.	Losartan	Hypotensor
Azithromycin	Antibacterial	Meclofenamic acid	Anti-inflammatory
Astemizole	Antihistaminic	Mirtazapine	Antidepressant
Azathioprine	Immunosuppresant	Olsalazine	Gastric protector
Benzocaine	Anaesthetic	Omeprazole	Gastric protector
Butabarbital	Sedative	Paramethadione	Anticonvulsant
Carbinoxamine	Antihistaminic	Phenelzine	Antidepressant
Cyproheptadine	Antihistaminic	Phenobarbital	Anticonvulsant
Danazol	Androgen	Procaine	Local anesthetic
Dichlorphenamide	Carb.Anhydr.Inhibitor	Pyridoxine	Vitamin
Dixyrazine	Neuroleptic	Pyrimethamine	Antimalarial
Flucytosine	Antifungal	Quinapril	ACE inhibitor
Fluvoxamine	Antidepressant	Salicylates	Analgesic
Ganciclovir	Antiviral	Saquinavir	Antiviral
Ketoconazole	Antifungal	Sotalol	Beta blocker
Lincomycin	Antibacterial	Trimethadione	Anticonvulsant
Lisinopril	Hypotensor		

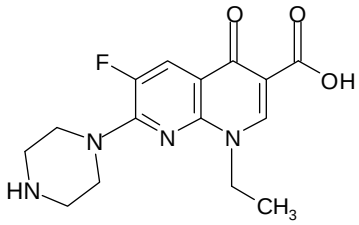
FLUOROQUINOLONES

Among the phototoxic drugs in Table I, two groups have received special attention, namely quinolone antibiotics and non-steroidal antiinflammatory drugs.

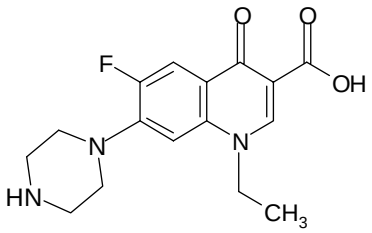
Quinolone antibiotics bearing fluorine substituent are commonly called fluoroquinolones (FQ). In despite of some adverse side-effects on which several reviews have been published recently (Ball et al., 1995; 1999) (Stahlmann et al., 1999) (Lipsky et al., 1999), the promising therapeutic activities shown by these compounds have encouraged the development of up to three generations of FQ. Chemically the parent compound is nalidixic acid. Some derivatives maintain the naphtyridinecarboxylic nucleus (enoxacin, trovafloxacin) but in others is replaced by the quinolinecarboxylic acid (norfloxacin, lomefloxacin, sparfloxacin, clinafloxacin, ciprofloxacin) in both cases the nucleus is substituted with halogens in one or two positions. Also is common the presence of piperazynil group as a substituent.



Nalidixic Acid



Enoxacin

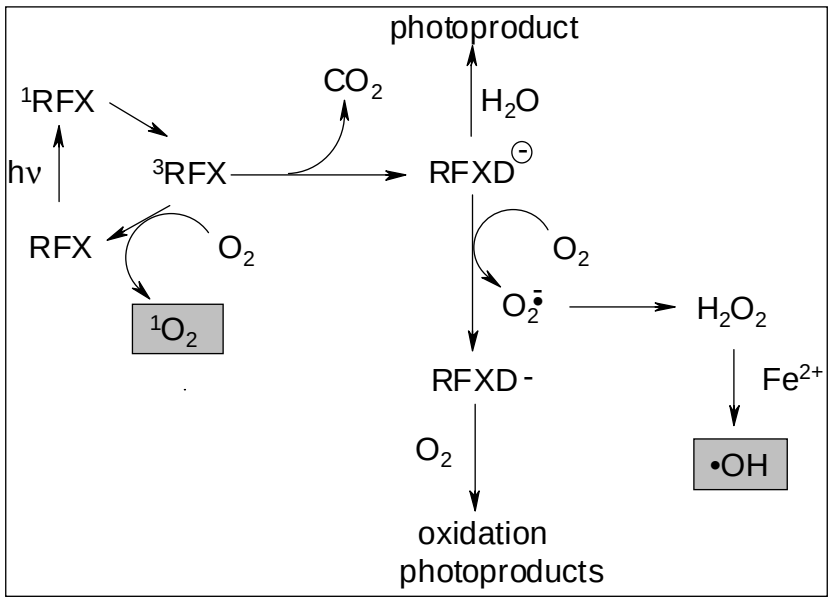


Norfloxacin

This pharmacological class has a broad-spectrum against gram-positive or gram-negative bacteria (Neu, 1990). Newer FQ, such as clinafloxacin, grepafloxacin, levofloxacin, sparfloxacin, tosufloxacin and trovafloxacin, are characterized by markedly improved activity against Gram-positive bacteria, e.g. pneumococci and enterococci, and also better activity against organisms such as mycoplasmas and chlamydiae (Goldstein, 1996) (Norrby, 1997) (Andriole, 1999). FQ act on the bacterial topoisomerase DNA gyrase (Domagala et al., 1986) having been suggested that quinolones bind DNA-gyrase complex via a magnesium ion inhibiting bacterial growth (Palù et al., 1992). The indexes of tolerability to FQ, mainly in the third generation, is claimed to be very high so that there is no significant difference between FQ and other antimicrobials in most double-blind studies (Stahlmann et al., 1998). Thus, apart from the temafloxacin syndrome, it is considered that FQ adverse effects are usually mild and reversible (Ball et al., 1999). Nevertheless, the therapeutic use of FQ is limited in part because of the side-phototoxic effects reported widely in the literature (see references cited in Fasani et al., 1998) and the photomutagenic and/or carcinogenic effects indicated in some cases (Chetalat et al., 1996) (Klecak et al., 1997) (Johnson et al., 1997) (Maekinen et al., 1997) (Urbach, 1997) (Reavy et al., 1997). Mutagenic effects induced by FQ have been reported even in the dark (Domagala, 1994). In general it can be assumed that phototoxicity has not to be a necessary factor regarding a possible photomutagenic risk (Loveday, 1996). In the case of FQ, some results obtained from the *in vitro* Chinese hamster V79 cells assay indicate a similar ranking for phototoxic and photomutagenic potencies (Snyder et al., 1999). Mutagenicity effects found for phototoxic FQ appears to indicate shared mechanistic routes. Thus, currently a number of works are made dealing with the mechanisms of photosensitization induced by FQ in an attempt to explain phototoxic and genotoxic effects.

Photoxicity and photomutagenicity induced by FQ appears to be related with structural features (Ball et al., 1995) (Lietman, 1995). 8-Halogenated FQ (i.e., lomefloxacin, clinafloxacin) provoke severe reactions in the skin in comparison with the low phototoxicity exhibited by 8-methoxy derivatives (Marutani et al., 1993) (Domagala et al., 1994) (Rosen et al., 1997a). Moreover, fluorine substituent to the 8-position of quinoline ring of FQ also induces photoallergic responses (Marutani et al., 1998). In general, the presence of an electron-donating substituent has been suggested to confer photostability to the halogenated substituent at the position 8 reducing the phototoxicity (Yoshida et al., 1996). Although the exact mechanism of FQ photosensitization remains unclear, basically, the following processes have been indicated to justify the FQ photoreactivity: i) oxygen singlet produced by the zwitterionic form resulting from dissociation of carboxylic acid and simultaneous protonation of the piperazinyl group (Bilski et al., 1996). ii) the formation of reactive oxygen species including singlet oxygen, superoxide radical, hydroxyl radical and hydrogen peroxide (Wagai et al., 1991, 1992a, 1992b) (Iwamoto et al., 1992) (Rosen et al., 1997b) (Umezawa et al., 1997) (Morimura et al., 1997), although; a mechanism based on these toxic agents does not appear to be correlated with the FQ photoreactivity (Umezawa et al., 1997) (Martínez et al., 1998); iii) the dehalogenation photochemically induced generating a highly reactive carbene C-8 which reacts with some cell component (Martínez et al., 1997, 1998); iv) a combinated process wherein the homolytic defluorination leading to the formation of aryl radical which triggers the attack to the cellular substrate whereas the oxygen reactive species could operate either in a secondary or in a parallel process (Fasani et al., 1998). Similar conclusion has been reported in the study of effects of

photoactivated lomefloxacin on cultured adult rat liver cells. In this case, 8-oxo-7,8–dihydro-2'-deoxyguanosine fomed is attributed to the simultaneous Type I and Type II photosensitization (Rosen, 1997c). The defluorination is believed to proceed via the triplet state corresponding to the zwitterionic species resulting from protonation of the piperazinyl group and the dissociation of carboxylic acid (Sortino et al., 1998). Identical point of view is adopted in the study of the photodegradation of rufloxacin (RFX) which presents a strong dependence on the pH (Condorelli et al., 1999). Moreover the presence of oxygen is proved to mediate in UVA-induced damage in membranes as observed in red blood cell hemolysis and lipid peroxidation. These results are interpreted in terms of simultaneous Type I (radical mediated) and Type II (oxygen mediated) reactions according to the following scheme (Condorelli et al., 1999).



An important aspect of this issue is the localization and the accesibility to the targets for the photosensitisers and/or the photoproducts. Thus, the structural and physicochemical properties, kinetic, metabolism and the photophysics and photochemistry of the photosensitisers are usually invoked to explain the molecular mechanism of phototoxicity *in vitro*. However, it has been claimed the influence of the biological environment on the phototoxicity mechanisms (Aveline et al. 1999). In the same context, reactive oxygen species generated from the photoactivation of some FQ are proved to attack DNA (Snyder et al., 1999) or induce lysosomal membranes damage (Ouedraogo et al., 1999) but that only could occur assuming that those species are generated inside the cell at the site wherein exert its action. Therefore, cell permeation, hydrophobicity, metabolization and subsequent subcellular localization appear to be critical factors to contribute to phototoxicity.

NON-STEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

NSAIDs is a chemically heterogeneous group of drugs mainly used as antiinflammatory particularly in the treatment of rheumatic diseases. Basically, three sub-class may be considered simply taking as a reference chemical group presents in the molecule, i.e.; carboxylic acids (salicylates, arylalkanoic acids and fenamates), pyrazoles and oxicams (Condorelli et al., 1996a). In any of these sub-class phototoxic and non-phototoxic molecules can be found. Thus, the different photoreactivity as a consequence of different structural patterns as well as the different phototoxic effects observed either *in vivo* or *in vitro* (Ljunggren, 1985a, 1985b) (Przybilla et al.,

1987a) (Kochevar, 1989) (Ophaswongse et al., 1993) may explain the high number of works devoted to the mechanistic aspects related with the photodecomposition of NSAIDs. In addition to that, the wide use of these drugs enhances the interest of the studies on the mechanisms involved in the NSAID-induced photosensitization reactions.

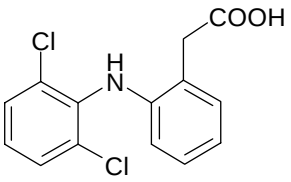
Among the NSAIDs, those compounds containing arylpropionic acid in its chemical structure have a considerable importance because of its extent use. It has been pointed out that such a use in the clinical practice has led to multiplier the number of reports about noxious photo-induced effects. The result is the existence of a number mechanistic studies on this subject. Benoxaprofen (not included in Table I), one of the most studied NSAID arylpropionic derivative, presents so acute phototoxic effects which have contributed to the removal of this drug from the European market in 1982. Naproxen is other typical representative compound of NSAIDs arylpropionic acid sub-class. It causes skin photosensitivity and DNA photocleavage (Diffey et al., 1983) (Artuso et al., 1990, 1991) (Condorelli et al., 1995) (Giuffrida et al., 1996). Phototoxic effects have been also reported for other compounds included in this sub-class such as ketoprofen (Przybilla et al., 1987b) (Costanzo et al., 1989b) (Mozzanica et al., 1990) (Nabeya et al., 1995), suprofen (Kurumaji et al., 1991) (De Guidi et al., 1994) (Castell et al., 1994a), (Gould et al., 1995) tiaprofenic acid (Diffey et al., 1983) (Ljunggren, 1985a) (Przybilla et al., 1987a, 1987b) (Boscá et al., 1992) (Castell et al., 1994a, 1994b) (Miranda et al., 1995) (Gould et al., 1995) and carprofen (Ljunggren, 1985a, 1985b) (Przybilla et al., 1987b) (De Guidi et al., 1993). The rest of sub-classes present photoreactivity although its incidence is significantly lower. Nevertheless, it is possible to find a number of works about the photosensitising properties of NSAIDs arylacetic group derivatives such as diclofenac (Ljunggren, 1985a, 1985b) (Przybilla et al., 1987a), pyrazol derivatives such as benzydamide (Motley et al., 1988) (Foti et al., 1992) (Goday et al., 1993). A particular case is tolmetin an arylacetic derivative for which there is any phototoxicity clinical report although it induces phototoxic effects *in vitro* (Giuffrida et al., 1995) (Boscá et al., 1998).

Several mechanistic aspects related to the photodecomposition of NSAIDs have been analyzed in the papers released since 1989 by the Department of Chemical Science in the University of Catania (Italy) (Costanzo et al., 1989a, 1989b) (De Guidi et al., 1993, 1994) (Giuffrida et al., 1995, 1996a, 1996b) (Condorelli et al., 1995). Likewise, a number of works dealing with the same subject have been made in the Department of Chemistry in the Polytechnic University of Valencia (Spain) including some in collaboration with other centers (Boscá et al., 1990, 1992, 1994, 1995, 1997) (Miranda et al., 1991) (Jiménez et al., 1997) (Encinas et al., 1998a, 1998b, 1998c) (Castell et al., 1992, 1994a, 1994b) (de Vries et al., 1997)

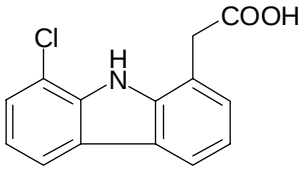
The photodegradation of relevant NSAIDs arylalkanoic derivative, naproxen, in aqueous neutral medium is characterized by the appearance of a solvated electron and a triplet state as proved by flash photolysis technique. So, two pathways are claimed to be responsible of the phototoxic effects (Miranda, 1992). The triplet state of photoexcited naproxen has been recognized as an effective singlet oxygen sensitizer. Besides, the solvated electron appears involved in the formation of free radical. In fact, ESR assays using spin trap MNP [2-methyl-nitroso-propane] indicate the presence of a H-MNP adduct and another C-centered radical. Those data have been interpreted by considering that decarboxylation is the first step in the photodegradation process (Moore et al., 1988) (Costanzo et al., 1989a) (Bosca et al., 1990) (Castell et al., 1993). The C-centered radical is considered to evolve to a peroxyl radical which degradates to first a secondary alcohol and then to the ketone as a final product. As included in cyclodextrin a marked predominance of alcohol over ketone has been reported (Jiménez et al. 1997). It must be considered that those photoproducts differentiate from the parent product with regard to its acidity. The photodegradation reaction changes the acidic functional group involves in the metabolization and clearance of naproxen. Affecting biotransformation and pharmacokinetic factors naproxen becomes a more hydrophobic compound with capability to link to hydrophobic areas such membranes wherein it exert its phototoxic effects (Moore, 1998) acting in a similar way to that reported for benoxaprofen photoproducts (Sik et al., 1983) (Kochevar et al., 1984).

NSAID acetic derivative diclofenac [2-(2-6-dichloroanilino)phenylacetic acid] is lesser phototoxic than naproxen. Nevertheless, this drug

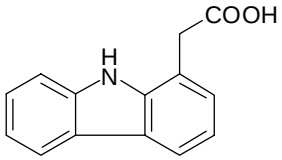
has received attention because of its wide use. A mechanistic study of the photodegradation is found in the recent literature (Encinas et al., 1998). The major photoproducts of diclofenac are carbazole derivatives (compounds 8Clcb and cb) presenting the chloro derivative (8Clcb) structural similarity with the phototoxic drug carprofen. In contrast to that found for naproxen the acid group remains in the diclofenac photoproducts.



Diclofenac



8Clcb



cb

The point arising from this system is whether the phototoxicity may be attributed to the chlorocarbazole compound (8Clcb) or the interaction with the biological substrate is originated by the free radical formed in the photodegradation of diclofenac.

Assays *in vitro* performed with Diclofenac and the photoproducts show positive photoxicity only for 8Clcb. Likewise, the analysis of the photophysical data are interpreted considering the participation of the triplet state of 8Clcb. Thermodynamic considerations as well as an observed quenching of triplet state as the concentration of 8Clcb is increased lead to formulate the formation of an excimer from which a radical ion could be formed. Dehalogenation is followed to yield an aryl radical and chloride anion. The results obtained in laser flash photolysis and ESR experiments seems to be in agreement with the mechanism suggested

MISCELLANEOUS. ARYLNITROSAMINES, ARYLAZODERIVATIVES, ARYLTRIAZENES AND ARYLHYDRAZINES

Some arylnitrosamines (Wakabayashi et al.; 1989) (Ohshima et al., 1989), arylazoderivatives (Stiborova et al., 1990) (Chung et al., 1992), aryltriazenes (Malaveille et al., 1982), arylalkyltriazenes (Thust et al., 1991) (Smith et al., 1996) and arylhydrazines (Toth, 1975, 1977, 1993) (Parodi et al. 1981) (Lawson et al., 1985) are genotoxic agents and have in common their capability to be metabolized to arenediazonium ions (Stiborova et al., 1988a, 1988b) (Smith et al., 1988) (Ohshima et al., 1989) (Thust et al., 1991) (Walton et al., 1997).

The salts of arenediazonium ions (ArN_2^+) are versatile compounds widely used in chemical synthesis (Zollinger, 1994). Some arenediazonium ions might be formed from the reaction in acid medium between sodium nitrite and a suceptible substrate coming from dietary component (Ochiai et al., 1984) or drugs such as bamethan (Kikugawa et al., 1987), acetaminophen (Ohta et al., 1988), etilefrin (Kikugawa et al., 1989) or synephrine (Fernández-Liencres et al., 1993), therefore the formation of arenediazonium ions *in vivo* is not unlikely. Moreover, it is known that edible mushrooms (*Agaricus bisporus*) contains arenediazonium ions as well as several precursors including some arylhydrazines (Levenberg, 1962) (Ross, 1982) (Chauhan et al, 1984) (Toth et al., 1989).

Most reactions involving arenediazonium ions are nucleophilic addition and dediazoniation

$$\begin{aligned} ArN_2^+ + R &\rightarrow Ar - N = N - R \\ ArN_2^+ &\rightarrow (Ar) + N_2 \end{aligned}$$

where the second reaction corresponds to the dediazoniation process which gives rise to the appearance of a reactive species (Ar) and releases dinitrogen.

The degradation of arenediazonium ions, known as dediazoniation, may occur via two types of mechanism, either heterolytic or homolytic. The latter requires the transfer of an electron from a reducing agent.

$$ArN_2^+ \xrightarrow{h\upsilon/\Delta} Ar^+ + N_2$$
$$ArN_2^+ \xrightarrow{e^-} Ar^\bullet + N_2$$

Both processes can occur simultaneously the heterolytic one can be activated thermal or photochemically whereas the second one is favoured by strong reductants (Galli, 1988).

Some aspects related with the electronic structure, dediazoniation mechanisms (García Meijide et al., 1998) (Glaser et al, 1999 and references cited therein) (Pazo Llorente et al., 1999) (Quintero et al., unpublished results) keep these subjects as active fields of research. In addition, the arenediazonium ions have demonstrated mutagenic effects and can also cause tumors in animals (Malaveille et al., 1982) (Ochiai et al., 1984) (Ames et al., 1987) (Ohta et al., 1988) (Ohshima et al., 1989) (Kikugawa et al., 1987, 1989, 1992) (Kato et al., 1992) (Lawson et al., 1995) (Toth et al., 1981, 1982, 1989, 1992, 1993, 1998) (Stiborova et al., 1999) but there is some discrepancy about the ultimate genotoxic agent. In this context, it has been suggested the possible direct action of arenediazonium ions (Chin et al., 1981) (Hung y Stock, 1982) (Koepke et al., 1990) (Gannett et al., 1999). On the other hand, mutagenic and carcinogenic effects have been also attributed to aryl radicals formed in a homolytic reaction (Berh, 1989) (Griffiths et al., 1992) (Kikugawa et al., 1992) (Kato et al., 1992) (Hazlewood et al., 1995) (Lawson et al., 1995) (Hiramoto et al., 1995) (Gannett et al., 1996, 1997). Besides aryl cation originated in heterolytic dediazoniation has been also suggested as genotoxic agent (Malaveille et al., 1982).

It is worth noting that apparently arenediazonium ions could be considered as good candidates to behave as photosensitizers. Although the aromatic substituents have a strong influence on the reactivity of arenediazonium ions, in general, they are photolabile compounds which descompose by action of UVA-Vis radiations to give an aryl cation (Ando, 1978). The aryl cation is so highly reactive species which result difficult its detection (Gasper et al., 1995) (Steeken et al., 1998). Thus, in a physiological medium, aryl cation will react likely with water but it is also probable to react with other substrate present in their vicinity (Behr, 1989) (Ayra et al., 1993). In addition, arenediazonium ions could remain accumulated in plasma taking account their ability to form azo coupling adduct with tirosyne and histidine residues of proteins (Tracey et al., 1997). Moreover, arenediazonium ions have shown to be capable to induce the peroxydation of lipids (Einsele et al., 1987) (Preece et al., 1989)

Antineoplastic drugs, vinblastine, fluxoridine, fluorouracil, flutamide, methotrexate or dacarbazine are recognized as phototoxics. One of them, dacarbazine is an imidazole dimethyltriazene [5-(3,3-dimethyl-1-triazenyl)-1H-imidazole-4-carboxamide] introduced into clinical practice in the 1970s which remains as a reference drug in the treatment of metastatic melanoma. It is known that the light descomposes this compound originating photoproducts responsibles of the phototoxic effects (Stevens et al., 1978) (Baird et al., 1978) (Horton et al., 1979). However a very little information is found in the literature with regard to the phototoxicity induced by precursors of arenediazonium ions. Antitumour drugs such as 3-(haloethyl)aryltriazenes (Lown et al., 1982), diaryltriazenes (Lassiani, et al., 1990), dimethylphenyltriazenes (Foster et al., 1993); antiprotozoal drug diminazene used in association with Pt as cytotoxic drug (González et al., 1997); hydrazine derivatives used as antithrombotic and vasodilating drugs (Rehse et al., 1998); phenylazo derivatives with antitubercular activity (Vazzana et al., 1993) are some examples of drugs which present chemical structures for which, in principle, a possible metabolization to arenediazonium ions could be expected.

All of the data mentioned above suggest that photostable precursors could afford the formation of arenediazonium ions. Subsequent photoinduced formation of reactive species from arenediazonium

ions could add unwanted interferences in a system wherein therapeutic and mutagenic effects can occurs associated. The coincidence of therapeutic and mutagenic effects, common in several triazenes compounds (Curtis et al., 1984), and the lack of information about possible synergistic effects in mutagenic damage as a result of the combination of alkylating agent (Sanderson et al., 1996) are important difficulties for this kind of drugs to be used safely. In fact, distinguishing between metastatic tumour and secondary malignancies induced by antitumour agent is very complicated in many cases. Thus, phototoxicity is possible to be just a minor inconvenience regarding the importance and severity of the other side-reactions but studies should be made in order to evaluate the possible contribution of photoactive intermediates in the therapeutic or toxic activities of drugs potentially precursors of arenediazonium ions.

CONCLUDING REMARK

In the present paper, a review has been made in relation with the mechanisms involved in drug phototoxicity. As can be easily understood, it is not conceivable to include all of the results obtained about this subject even being limited to recent years. Thus, only relevant data have been picked up from the literature with regard to mechanistic aspects associated to drug-induced phototoxicity.

The current status in this field appears to be characterized by a significant dispersion in relation with methodology, results and assessment of these results. This situation could be parallel to the difficulty to obtain reliable data from animal or human tests as well as from clinical epidemiologic studies (Spielmann et al., 1995).

With regard to the mechanistic pathways, it is accepted basically the four paths as main routes for phototoxic reactions, namely singlet oxygen formation, radical formation, covalent photobinding and production of photoproducts in decomposition reaction. However, several possibilities combinating these elements along with the inclusion of unusual routes composes a very complicated picture. Thus, any attempt to reduce the mechanistic aspects to a formal assortment becomes a rough approach to the experimental behaviour. The differences found in the phototoxic mechanisms appears linked, in principle, to structural features which may differ from one molecule to other even in the molecules pertaining to the same chemical group. In fact, structural factors determine the ability to absorb radiation, the probability to reach triplet state, the bonding breakage in homolytic or heterolytic processes, the stability of photoproducts, etc. Nevertheless, significant mechanistic variations must be expected depending on the environment in which the photosensitization occurs, the localization of the photosensitizers or the accesibility of the targets. These circunstamces have been pointed out in the recent literature (Martínez et al., 1998) (Bilski et al., 1998) (Snyder et al., 1999) (Ouedraogo et al., 1999) (Aveline et al., 1999). Likewise, it is worth noting that the phototoxic effects could be enhanced or quenched in particular cases as a result of interferences coming from medication, individual suceptibility, etc.

In relation to the drugs which could act potentially as arenediazonium precursors a limited information about their phototoxicity is found in the literature although possible unwanted interferences could be expected.

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