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Light and drugs: practice and clinical perspectives

by Professor Beverley D Glass

The effect of light on drugs has, until recently been considered relatively unimportant, even though the storage instruction *Protect from Light* is being prescribed by the pharmacopoeias for an increasing number of drugs and excipients.¹ Despite the fact that there has been much publicity over the years about the incidence of skin cancers especially in countries such as Australia, there has been limited awareness raised about the combined effect of light and drugs on the human skin.² Although therapeutic inactivity is not a likely outcome, it is important to consider that even minor photodegradants may result in light-induced side-effects³ e.g. photosensitivity reactions in patients.

Photosensitivity may be defined as an adverse reaction to light, which may be phototoxic or photoallergic in nature.⁴

Knowledge of light and drugs allows the pharmacist to offer advice on:

- Handling, packaging, labeling and distribution of drug products
- Adverse effects (photosensitivity reactions)
- Therapeutic aspects and new drug delivery systems.

Drugs may be exposed to a variety of light conditions, including direct sunlight, filtered (window) sunlight and various artificial light sources during manufacture, storage, distribution and administration to the patient. Although the ultraviolet (UV) component of sunlight is considered the most problematic, exposure to fluorescent lighting for prolonged periods of time needs to be taken into consideration in terms of the spectral distribution of these light sources, which extends from 300nm to 3000nm. UV-C (200-280nm), UV-B (280-320nm) and UV-A (320-400nm) comprise the three regions of the UV-spectrum. Although eliminated from the earth's surface by absorption by molecular oxygen and ozone, UV-C, which may cause adverse effects, is present in artificial light sources such as germicidal lamps and welding arcs. Although the UV-A reaches the earth's surface to a greater extent than that of UV-B, it is the UV-B which causes sunburn and skin cancer. While sunlight and fluorescent light sources have a high output

Learning objectives

After reading this article you should:

- Differentiate between photoallergic and phototoxic reactions in patients.
- Recognise drugs with the potential to degrade on exposure to light during handling, storage and distribution.
- Recognise drugs with the potential to cause photosensitivity reactions in patients.
- Recommend management strategies to ensure the stability of drug products and to prevent and treat photosensitivity reactions in patients.

in the visible region of the spectrum (400-800 nm), the significant output in the UV-region must be noted for the fluorescent light sources. Most drugs absorb UV-C, while UV-B is responsible for the photoreactivity of drugs in the presence of sunlight and UV-A in addition to being absorbed by DNA, may cause photosensitisation reactions. In order to cause a reaction, the UV radiation must penetrate, whether it is the drug in the formulation or in the patient. The former is dependant on the transparency of the packaging. In the patient, although UV radiation shorter than 320nm penetrates the stratum corneum of the Caucasian skin, it must reach the absorbing drug molecule in the peripheral blood capillaries in order to illicit a photochemical response.⁵

Requirements for a drug to be considered as having a potential to cause photosensitivity reactions in a patient:^{6,7}

- *The drug and/or metabolite/photodegradant must be present in the tissues at the body surface such as the skin, eyes and/or hair.*
- *The drug must be in a sufficiently high accumulative dose.*
- *The drug must degrade on exposure to light forming degradants and/or metabolites which are susceptible to photodegradation.*
- *The drug must contain chemical functions which are known to be photoreactive.*

Studies into the photoreactivity of drugs provide us with important information about the potential for photosensitivity effects in patients, instructions for

Table 1: Chemical functions and photoreactivity.⁸

Description	Chemical function
-Carbonyl group	-C=O
-Nitroaromatic group	Ar-NO ₂
-N-oxide group	-N → O
-Double bond	-C=C-
-Aryl chloride group	Ar-Cl
-C-H bond at a benzylic position or α to amine-N	-N-CH ₂ -
-Sulfides, phenols	-SH, -OH

packaging and storage and also alert us to the possibility of in-use photostability. In-use photostability must be considered when pharmacists repack drugs and/or patients remove drugs from the original/manufacture's container.

1. Photoreactivity of drugs

It is possible to predict the photoreactivity of drugs based on certain molecular features, which are likely to make the drug photolabile. It should also be noted that a drug which displays photoreactivity *in vitro* does not necessarily give rise to adverse photosensitivity effects in patients.

Several chemical functions are capable of introducing photoreactivity into drugs (Table 1).

Case study

A patient supplied with a chloroquine syrup in a rural and remote location returns to the clinic a few days later with a query. Due to the lack of availability of a liquid dosage form at the clinic, the syrup has been extemporaneously compounded using chloroquine tablets, a suspending agent (sodium carboxymethylcellulose), syrup and compound hydroxybenzoate solution APF in a clear glass medicine bottle. The patient is concerned that the syrup has undergone a color change from white to yellow.

Although these chemical functions are present in a large variety of drugs, the photostability of these drugs is dependent on absorption of ambient light at >330nm and is also dependent on the dosage form, which may be a concentrated solution or in the solid-state, and thus photoreaction may be too slow to be of practical

importance, as opposed to dilute solutions where degradation may be rapid. Although drugs degrade to different extents on separate exposure to heat, moisture, air (including oxidation) and light, combinations of these stresses can cause complex behaviour. The pharmacist needs to be aware that photodegradation can be accelerated by heat and thus storage instructions to patients in tropical climates are important. In drug formulations, the presence of excipients adds further complications because the excipients may increase, have no effect on, or decrease the inherent stabilities of the drug.⁹

However, even a drug in the solid-state may undergo a color change (reactions take place only in a thin surface-layer) on exposure to light and different polymorphic forms of a drug may degrade at different rates.¹⁰ This change in color might not relate to chemical degradation of the drug; however the ability to effect changes in the physical stability such as tablet hardness, friability, disintegration and dissolution needs to be considered due to the potential changes in bioavailability and thus therapeutic efficacy. However preparation of liquid dosage forms may also result in a change in the polymorphic form of the drug substance. Drug products intended for use in areas such as tropical north Queensland are exposed to severe conditions of light, heat and moisture and are required to maintain stability e.g. the antimalarial drug, chloroquine which although most frequently used as tablets is also formulated as an injection, solutions and syrups¹¹ and is susceptible to photodegradation.

Management strategies for patients and other health professionals about drugs susceptible to photodegradation should include:

- Storage instructions in respect of heat, and exposure to air and light.
- Instructions re removal of the drug product from its original container or removal of an outer cardboard sleeve.

The pharmacist also has a role to play in monitoring the distribution channel and storage of drugs by health professionals in rural and remote locations.

2. Photosensitivity effects of drugs

Phototoxicity and photoallergy are the two major types of photosensitisation. Phototoxicity occurs more frequently than photoallergy and does not involve an immunological mechanism. Phototoxic reactions, which resemble severe sunburn and may even blister, are dose dependent for both drugs and sunlight. These reactions occur immediately after, or within a few hours of taking the drug and simultaneous exposure to radiation of the appropriate wavelength (usually from 300-400nm) and

will subside if the drug is withdrawn and/or if possible the patient avoids excessive exposure to sunlight. Phototoxicity may cause damage to cells by modification of certain targets such as DNA, lipids and/or amino acids and proteins. Photoallergy is immune-mediated, whereby the drug, on exposure to radiation, combines with a protein or perhaps a biomacromolecule in the skin to form an antigen, leading to an immune response. Photoallergic reactions are not dose dependent and require several exposures and an induction period. The low incidence of photoallergic reactions may be attributed to the body's immune response mechanisms. Photoallergy has a different histology compared to that of phototoxicity, manifesting as eczematous, lichenoid, urticarial, bulbous or purpuric rashes.¹²

Table 2, although not comprehensive, represents the topical preparations, major systemic drug classes and those drugs within these classes most frequently implicated in photosensitivity reactions. Although these drugs represent a wide variety of chemical structures, there are certain general characteristics which these drugs have in common, including:¹³

- Low molecular weight (200-500 Daltons)
- Planar, tricyclic or polycyclic structures
- Heteroatoms for resonance stabilisation
- Absorption of UV and / or visible radiation.

Table 2: Drugs implicated in photosensitivity reactions^{12,13}

Topical preparations	
Antihistamines, antiseptics, coal tar derivatives, sunscreens, retinoid topicals	
Systemic drugs - class	Drugs
NSAIDs	<i>Naproxen, ketoprofen, piroxicam, diclofenac</i>
Diuretic drugs	<i>Hydrochlorothiazide, frusemide, chlorothiazide</i>
Antipsychotic drugs	<i>Chlorpromazine, prochlorperazine, chlorprothixene</i>
Antibacterial drugs	<i>Demeclocycline, nalidixic acid, sulphamethoxazole, ciprofloxacin, oxytetracycline, doxycycline</i>
Antimalarial drugs	<i>Chloroquine, quinine, mefloquine</i>
Antidepressant drugs	<i>Amitriptyline, trimipramine, nortriptyline, doxepin</i>
Cardiovascular drugs	<i>Amiodarone, nifedipine, captopril, enalapril</i>
Hypoglycaemic drugs	<i>Glipenclamide, tolbutamide, chlorpropamide</i>
Anticonvulsant drugs	<i>Carbamazepine, lamotrigine, phenobarbital</i>
Antihistamine drugs	<i>Cyproheptidine, diphenhydramine, triprolidine</i>

Although it may be possible to some extent to predict the photodecomposition of drugs related to their molecular structure and alert the pharmacist to potential problems in packaging and storage and adverse effects in patients, there has been no reported relationship between chemical structure and photosensitivity effects in patients.

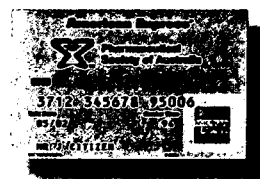
Topical agents such as antihistamines, antiseptics, coal tar derivatives, sunscreens and more recently retinoid creams have been implicated in photosensitivity reactions. Phototoxicity has been reported

on application of coal tar preparations,^{14,15} while photo-contact dermatitis may be attributed to some sunscreens. Since both the UV-A and UV-B ranges of the spectrum need to be covered, a broad spectrum sunscreen is recommended to include a cinnamate ester (UV-B) and a benzophenone such as 4-methoxy-2-hydroxybenzophenone (UV-A). Both of these compounds absorb sunlight energy, whereas titanium dioxide and zinc oxide provide barrier protection. Titanium dioxide¹⁶ is reported to block UV-A and UV-B (to 340 nm), whereas zinc oxide



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because of its larger particle size covers both the UV and visible ranges. More recently Pinnell, et al^{17,18} have reported on the properties of microfine zinc oxide both in terms of its superior sun protection when mixed with octyl methoxycinnamate (and photostability) and when compared to that of microfine titanium dioxide. It is important that sunscreens do not undergo photodecomposition as even stable photoproducts formed in very low concentrations may produce significant toxic effects during actual sunscreen usage. Because of this concern the use of p-aminobenzoic acid (PABA) has declined significantly as reports on the production of reactive intermediates on exposure to light, with subsequent reaction with oxygen forming oxidants is known to produce toxic effects.

Photosensitising mechanisms may be photophysical and /or photochemical in nature. For photosensitisation to occur, it is a requirement that there is an overlap between the absorption spectrum of the drug and the incident light energy with wavelengths of <300nm implicated to a greater extent in these reactions. Nonsteroidal-antiinflammatory, diuretic and antibacterial drugs are considered significant as photosensitising drugs and a photochemical basis for this reactivity has been determined. In addition, the reactivity of many photosensitising drugs across the pharmacological classes has been attributed to the presence of an aromatic chlorine (Ar-Cl) substituent as illustrated in figure 1 for frusemide, hydrochlorothiazide, chlorpromazine and chloroquine. In these reactions, this bond is dissociated (photodehalogenation) with the liberation of HCl and a mixture of reduction and substitution products. For chlorpromazine, it has been reported that, in addition to the degradants formed on exposure to light, a decrease in pH is observed¹⁹ with the liberation of HCl reported to contribute to a decrease in pH. These findings explain the sensitivity, inflammation or dermatitis that usually precedes the deposition of melanin in the skin of patients treated with large doses of this drug. It must be noted that not all chloroaromatic drugs undergo this type of reaction with a notable exception

Figure 1: Drugs implicated in photosensitivity reactions – chlorine substituents

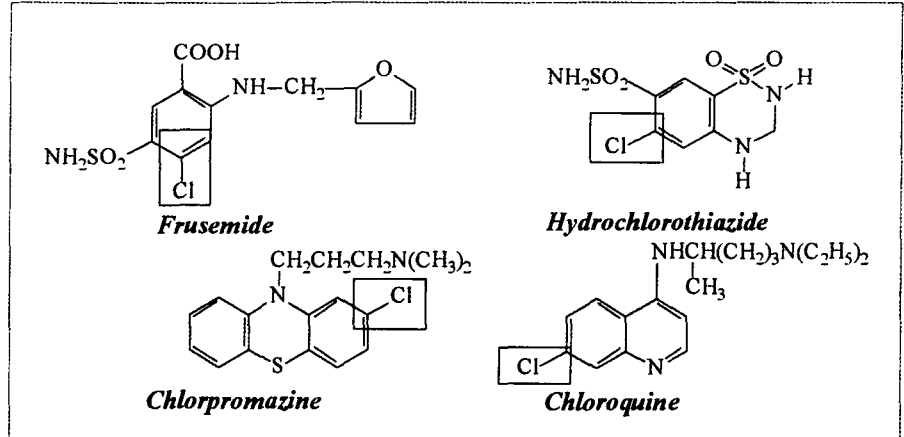
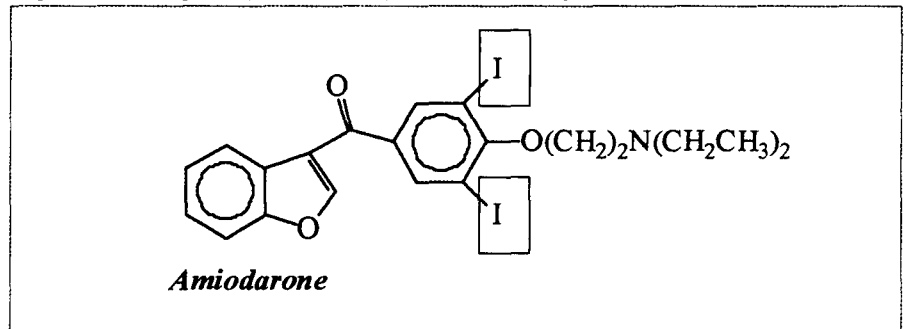


Figure 2: Drugs implicated in photosensitivity reactions – amiodarone



being chlordiazepoxide, which although implicated in photosensitivity reactions does not undergo photodehalogenation. Because the chlorine-containing drugs are frequently implicated in photosensitivity reactions, it must be said that the liberation of free radicals plays a major role in these adverse effects experienced by patients.

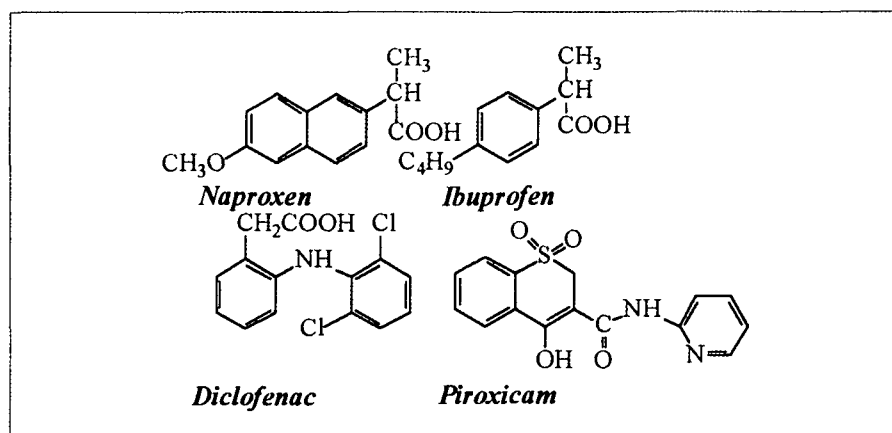
Amiodarone photosensitivity in patients has been reported to be dose-related^{20,21} with the slate blue²² discoloration on sun-exposed areas attributed to the deposition of lipofuscin, a product of lipid peroxidation.²³ The photochemical mechanism may be explained by photodehalogenation (removal of the iodine – Figure 2) with the aryl radicals formed, extracting hydrogen from linoleic acid and leading to peroxy radical formation.

Case study

Mr HM comes into the pharmacy to ask about sun protection. He is a keen surfer and is currently spending a lot of time on the beach in Cairns. He is concerned that areas of his skin not covered by his wetsuit are more prone than usual to sunburn even blistering. When asked Mr HM responds that he is not using a broad spectrum sunblock and that he has been taking naproxen for the last week, recommended to him because he has been having some trouble with his knee.

In the case of the nonsteroidal anti-inflammatory drugs (NSAIDs – Figure 3), it is often described as ironic that drugs designed to prevent inflammation result in inflammation due to photosensitivity

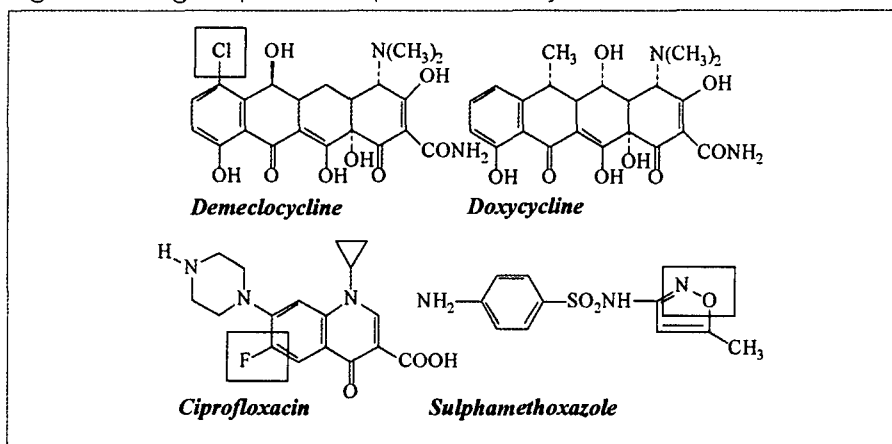
Figure 3: Drugs implicated in photosensitivity reactions – NSAIDs



there have been some photosensitivity reports on use of celecoxib, etodolac and rofecoxib. (etodolac and rofecoxib are not available in Australia)

The most photoactive in this class of drugs are the 2-arylpropionic acid derivatives such as naproxen due to removal of the carboxyl group (-COOH – photodecarboxylation) occurring. Although ibuprofen has been reported to be a photosensitiser, its absorption spectrum is weak. However the availability of both ibuprofen and naproxen without a prescription has led to widespread use and presents a role for the pharmacist in counselling patients about potential photosensitivity effects on excessive exposure to sunlight. In addition to being able to produce free radicals, the 2-arylpropionic acid derivatives can produce significant yields of singlet oxygen (the oxygen molecule in an excited singlet state – the ground state of oxygen is the triplet state³). Singlet oxygen and free radicals thus generated may photooxidise biological substrates such as membranes, lipids and proteins disrupting cells and causing oxidative stress and adverse reactions such as photosensitivity effects.²⁴ Singlet oxygen yields for naproxen are significant and this together with an efficient decarboxylation process should alert the pharmacist to a need for patient counselling. Some photosensitivity effects have been reported in patients taking piroxicam.^{25,26} However, there is some controversy as to whether

Figure 4: Drugs implicated in photosensitivity reactions – antibacterials.



reactions and in fact while gastric irritation is often the major side effect of this drug class, many patients present

with photosensitivity responses. Although the issue of gastric irritation has been addressed in the newer drugs in this class,



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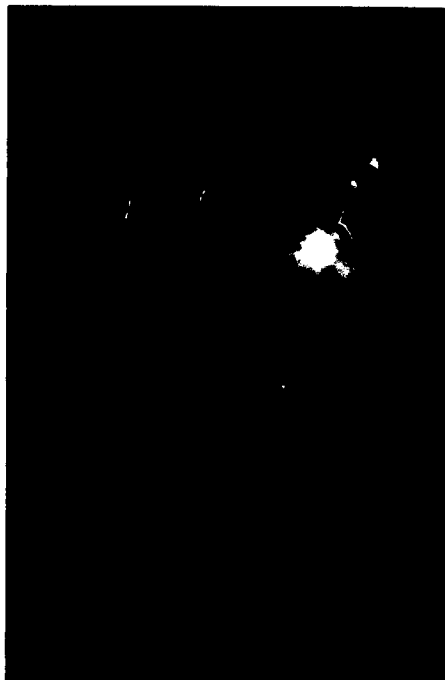
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concentration needs to be taken into consideration in photosensitivity reactions and this involves the dosage of drug concerned.

this may be attributed to a metabolite of piroxicam, due to the fact that there is no correlation between the in vivo and in vitro findings or the photo-oxidation process.^{27,28} In the case of diclofenac, after photodehalogenation (removal of both chlorine atoms) takes place, the carboxyl group remains intact which allows the photoproduct to be readily excreted. Drug concentration needs to be taken into consideration in all photosensitivity

reactions and this involves the dosage of the drug concerned – the higher the dose the higher the circulation concentration of the drug and the greater the potential for a photosensitivity reaction to occur. This needs to be taken into consideration when comparing the ability of naproxen and diclofenac to cause photosensitivity effects in patients.

In the antibacterial class of drugs (Figure 4), the tetracyclines especially demeclocycline (effective generator of singlet oxygen and free radicals – now rarely used) and oxytetracycline have been prominent in reports on photosensitivity reactions due to their extensive absorption spectrum in the UV-A region. Although these two have been largely replaced by doxycycline and minocycline, which have resulted in fewer phototoxic effects, some sunlight-induced pigmentation may still occur on exposed skin.²⁹ Again the dosage regimen of these drugs needs to be taken into consideration, not only in terms of drug concentration but also the duration of the regimen especially when doxycycline is used in malaria prophylaxis. For the fluoroquinolones, photodehalogenation, in this case cleavage of the C-F bond may produce radicals which can cause similar cell-mediated damage to that of their chlorinated counterparts.³⁰ When cotrimoxazole was found to cause photosensitivity effects in patients, it was proposed that sulphamethoxazole was causing these reactions due to cleavage of the N-O bond.

Management strategies for prevention and treatment of photosensitivity reactions in patients should include:¹³

- Use of a broad spectrum sunblock.
- Avoid excessive exposure to sunlight, and wear suitable protective clothing and eyewear.
- Treat sunburn-like reactions with emollients/oatmeal baths, soothing creams and gels.
- Treat inflammation with:
 - Topical corticosteroids²² (such as hydrocortisone) may be recommended up to three times per day, however issues such as the area concerned and the status of the skin are important considerations.
 - Antihistamines may be recommended (if urticaria is present) such as cetirizine 10mg orally, daily and if the urticaria persists and is non-responsive, the addition of a second antihistamine such as promethazine 25mg orally, at night may be considered.
- Withdrawal of the photosensitising drug if necessary.

Beverley Glass is Professor of Pharmacy at the James Cook University. She has been researching in the area of the photostability of drug molecules for 15 years and recently has focused on in-use drug stability and is interested in the clinical applications of light and drugs, especially photosensitivity effects and ocular phototoxicity in patients.

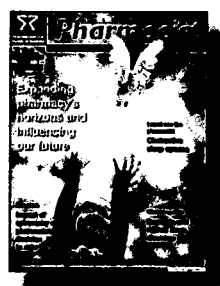


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Acknowledgement

The author would like to acknowledge the support and encouragement of Prof Doug Moore, a colleague, friend, and international authority in the area of the photostability of drugs.

Questions on page 157.

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