Photosensitivity: Light, sun and pharmacy

Mark L. Zammit BPharm(Hons), MSc(Agr Vet Pharm), Pg Dip Med Tox(Cardiff), MSc Med Tox(Cardiff), MEAPCCT

Principal Pharmacist, Clinical Pharmacy and Medicines & Poisons Information, Pharmacy Department, Mater Dei Hospital, Malta
Email: mark.l.zammit@gov.mt

Educational aims

- To provide an overview of different types of drug-induced photosensitivity reactions
- To provide an overview of treatment options and prevention strategies
- To provide an practical help as regards the use of sunscreens

Key words
phototoxic reactions, photoallergic reactions, photosensitivity reaction, sunscreen, sun protection factor

Light has a profound effect on us. We may not be conscious enough as regards the existences of many phototoxic substances and chemicals. A phototoxic substance is a chemical compound which becomes toxic when exposed to light. Phototoxicity may be manifested in various ways. Proper use of sunscreens may play a vital role in the prevention of many such reactions.

Introduction

The sun and the light that it emits are many times taken for granted, however light more precisely sunlight powers all life on earth, either directly or indirectly. Plants must have sunlight [or full-spectrum artificial light] to manufacture their food by photosynthesis. Plants, in turn, pass on their energy to the animals that consume them. Light is also essential for the survival of most animal species; even nocturnal animals require low-level light. Animals that have evolved in total darkness such as troglobites[cave dwellers] or deep-sea animals are often colourless, blind and cannot survive outside their natural environment.

For all diurnal species (species that are active during the day), including humans, light is important for many reasons. Obviously, it is required for vision. For many species of animals, full-spectrum light is required for the conversion of cholesterol to vitamin D. Light and its changing cycles – photoperiodicity; is used by animals to synchronize their biological clocks. Light is indeed important for the psychological well being of animals.

However the effect of light on humans is much more complex than we think. It influences us in ways we many times do not expect or understand. At least one study has suggested a direct correlation between higher rates of breast cancer in women and the night time brightness of their neighbourhoods.[1] It is in fact postulated that this is at least partly due to a dramatic alteration in the lighted environment from a sun-based system to an electricity-based system. Increasingly, the natural dark period at night is being seriously eroded for the bulk of humanity.[2] Based on the fact that light during the night can suppress melatonin, and also disrupt the circadian rhythm, it is proposed that increasing use of electricity to light the night accounts in part for the rising risk of breast cancer globally.[3] Light is nowadays being even considered as a public health issue.[4]

Photosensitivity and its epidemiology

In the context of pharmacy, an important effect of light is what is termed as photosensitivity. Drug-induced photosensitivity is termed as an undesirable pharmacological reaction in light irradiation.[5,6] Exposure to either the chemical or the light alone is not sufficient to induce the disease; however, when photoactivation of the chemical occurs, one or more cutaneous manifestations may arise. These include mainly either a phototoxic or a photoallergic reactions, but may also include a planus lichenoides reaction, pseudoporphyria, subacute cutaneous lupus erythematosus as well as hyperpigmentation, pigmentary changes or berloque dermatitis Photosensitivity reactions may result from systemic medications and topically applied compounds (Table 1).

Wavelengths within the UV-A (320-400 nm) range and, for certain compounds, within the visible range, are more likely to cause drug-induced photosensitivity reactions, although occasionally UV-B (290-320 nm) can also be responsible for such effects. UV-B wavelengths are most efficient at causing sunburn and nonmelanoma skin cancer.[9]

Photosensitivity eruptions typically occur in locations with prominent sun exposure such as in the face, extensor extremities, upper chest and back of neck. Characteristic

Table 1. Some medications and other substances associated with photosensitivity[7,8,6]	
Antibiotics	Ciprofloxacin and other quinolones, sulfonamides, dapsone, griseofulvin. Tetracyclines [especially demeclocycline; less frequently doxycycline, oxytetracycline and tetracycline; minocycline rarely]
Antihistamines	Dimenhydrinate, cetirizine, loratidine
Anti-inflammatories [NSAIDS]	Ibuprofen, naproxen, piroxicam
Anti-malarials	Chloroquine and related compounds (such as hydroxychloroquine), Sulfadoxine with pyrimethamine [Fansidar®]
Cardiovascular drugs	ACE inhibitors, amiodarone, amlodipine, clopidogrel, diltiazem, furosemide, losartan, nifedipine, statins, thiazide diuretics, sotalol
CNS agents	Carbamazepine, clomipramine, chlorpromazine, phenotiazines, tricyclic antidepressants, selegiline, zolpidem.
Miscellaneous	Acetazolamide, oral contraceptives and oestrogen, chemotherapy agents, ranitidine, sulfonylureas, tacrolimus
Topical agents	Deodorants in soaps; perfumes; coal tar products
Plants and herbs	Celery, giant hogweed, angelica, parsnip, fennel, dill, anise, parsley, lime, lemon, rue, fig, mustard, scurf pea, and chrysanthemums
Essential Oils	Fig leaf absolute oil; taget oil; vergena oil and verbena absolute oil; bergamot oil; cumin oil; lime (expressed) oil; angelica root oil; rue oil; opopanax oil; orange (bitter expressed) oil; lemon (expressed) oil; grapefruit (expressed) oil
Note: This list is NOT comprehensive. Manufacturers' package inserts should be consulted regarding potential photosensitivity of medications.	

sites of sparing include the upper eyelids, below the nose and chin, behind the earlobes and the finger-webs.

Photosensitivity reactions can be classified according to the underlying mechanism. They are the result of either phototoxicity or photoallergy. In patients who present with photosensitivity, it is often difficult to differentiate phototoxic from photoallergic reactions. However, they have a number of distinguishing characteristics (Table 2). Phototoxic reactions represent the most common form, whereas photoallergic reactions are generally uncommon.[6,10]

Phototoxic reactions may occur in almost any individual who received a high enough dose of the offending agent coupled with sufficient exposure to light irradiation.[11] The occurrence of drug-induced phototoxicity reactions can thus be dependent on the concentration or amount of the sensitising agent and the amount of light exposure.[11]

Phototoxic reactions

Phototoxic reactions are non-immunologic in nature. In these reactions the drug, after ingestion or topical application is believed to potentiate the solar energy by acting as a chromophore, causing absorption of ultraviolet light and causing damage to the skin tissue.[5]

Acute phototoxicity often begins as an exaggerated sunburn reaction with erythema and oedema that occurs within minutes to hours of light exposure; vesicles and bullae may develop with severe reactions.[9] The lesions often heal with hyperpigmentation, which resolves in a matter of weeks to months. Chronic phototoxicity may also appear as an exaggerated sunburn reaction. Lichenification often develops because of repeated rubbing and scratching of the photosensitive area.

Distinguishing phototoxic reactions from photoallergic reactions strictly based on physical appearance of the lesions may be difficult.[9] In contrast to photoallergic reactions drug-induced phototoxic reactions typically occur on first exposure to the drug, and they are often dose-related.[5,9,10] Cases of drug-induced phototoxic reactions are associated with a much quicker onset relative to cases of drug-induced photoallergy.[12] This could typically be within 30 minutes to several hours after exposure to UV light. In general phototoxic reactions are less severe than photoallergic reactions and resemble a severe sunburn.[12] The skin damage that occurs in phototoxic reactions is typically confined to areas of exposed skin only. Occasionally the nails may also be affected. The phototoxic effect is a well-known phenomenon referred to as photooncholysis.[7,12]

A classic example of a medicine associated with phototoxicity [sometimes also with photoallergy] is amiodarone, which induces photosensitivity in 10-50% of the patients treated with this drug.[6]

However some reports even mention rates as high as 75%.[13] As mentioned beforehand the development of phototoxicity is dose-dependent. It is reported that an amiodarone-induced phototoxic reaction depends on a total dose of amiodarone of 40g which is the minimal cumulative dose requirement. Under the regimens commonly used, photosensitivity can be expected after 4 months of continuous amiodarone treatment and appears to be unrelated to the skin type. Phototoxicity gradually decreases and returns to normal between 4 and 12 months after the withdrawal of amiodarone.[6]

Photo-onycholysis, or separation of the distal nail plate from the nail bed, is another manifestation of phototoxicity. Photo-onycholysis has been reported with

Table 2. Differentiating characteristics of phototoxicity and photoallergy[6,9,11,12]

Characteristic	Phototoxicity	Photoallergy
Frequency of occurrence	Common	Uncommon
Mechanism	Non-immune mediated	Immune mediated [Type IV]
Onset	Immediate (minute to hours) after exposure to drug and sunlight	May be delayed (hours to days) after exposure to drug and sunlight
Distribution	Usually confined to exposed skin	May affect unexposed skin
Potential for pigmentary changes	High	Low
Dose dependency	Yes	No
Potential for cross-reactivity	No	Yes
Potential for persistent light reaction	No	Yes
Clinical characteristics	Exaggerated sunburn	Dermatitis

the use of many systemic medications, including tetracycline, chloramphenicol, fluoroquinolones, oral contraceptives and mercaptopurine. Photo-onycholysis may be the only manifestation of phototoxicity in individuals with heavily pigmented skin.[9]

Photoallergic reactions

Unlike phototoxic reactions drug-induced photoallergic reactions are the result of an immunologic response. The proposed mechanism of photoallergic reactions is type IV cell-mediated hypersensitivity response.[5] It is postulated that when UV light reacts with either the drug or the drug's metabolites in the skin; this induces a structural change in the drug so that it behaves as a hapten.[5,10]. This hapten combines with proteins in the skin to form a hapten-protein complex [a compete antigen]. On subsequent exposure to the drug a hypersenistivity response is elicited.[10]. Once the patient is sensitised to the drug only minimal amounts of drug exposure are subsequently required to produce a photoallergic reaction.[5]

Photoallergic reactions are thus the result of cell-mediated immunity and require an initial sensitization period – an acute, subacute or chronic eruption which is usually described as a papulovesicular, eczematous and intensely pruritic rash generally appears 24 hours or more after exposure [onset can be anywhere from 24 to 48 hours to up to 14 days after sun exposure] this due to the fact that photoallergic reactions involve the immune system and there is typically a delay between the time of exposure to the drug and the actual onset of the skin eruption.[6,7,11] In general photoallergic reactions occurring in sensitised patients are not dose dependent.[12] Generally photoallergic reactions involve mainly direct sun-exposed areas but in severe cases may also affect areas that are normally protected from UV light.[6] Patients with photoallergic reactions should not take the offending drug again ever.

Pigmentary changes and berloque dermatitis

Other less common skin manifestations of phototoxicity include pigmentary changes. A blue-gray pigmentation is associated with several agents, including amiodarone, chlorpromazine, and some tricyclic antidepressants. Reactions to psoralen-containing botanicals (phytophotodermatitis) and drugs may resolve, with a brownish discoloration. Frequently, the pigmentary change is preceded by a typical sunburn reaction. If the reaction is not severe, some patients may not notice the erythema.

Pigmentary changes occur quite commonly as a manifestation of photosensitivity in patients receiving long-term high-dose amiodarone therapy.[13-18]

A blue-gray discoloration commonly develops on areas of skin that are subjected to unprotected light exposure due to deposition of amiodarone and its metabolites within the dermis. [3-16,18] Amiodarone-related hyperpigmentation develops after an average of 20 months of continuous amiodarone treatment and a minimal total dose of 160g amiodarone in about 8% of the patients, mainly of skin Type 1 - porcelain white skin. [Type 1 always burns and never tans. This type skin has the highest risk of skin cancer and wrinkles more readily than other types. Most Type 1 skin owners will have red or pale blonde hair, be blue-eyed and have freckles].[13-18]

A specific form of hyperpigmentation is what is termed as berloque dermatitis. The clinical presentation of berloque dermatitis may be classically divided into two phases. The initial acute inflammatory phase consists of erythema, oedema, pain, pruritus, and increase in skin temperature around the area of contact with the phototoxic agent. The second stage is hyperpigmentation of the lesion with patients typically presenting with small areas of redness or pigmentation of the skin, usually on sun-exposed areas. A careful history may reveal use of a perfume or fragrance-containing product on the skin prior to a period of sun exposure, such as

sunbathing or a picnic. If untreated, the natural history of the disease is biphasic; the inflammatory lesions resolve in days to weeks, but the pigmentation may last months or even years.[19]

Bergapten, or 5-methoxypsoralen, is the photoactive component of bergamot oil from the bergamot lime (Citrus bergamia), which is a popular ingredient in perfumes and fragrances. Apart from its existence in cosmetics and other toiletries it may also be found in soap, household cleaners, detergents, air fresheners, and other related items. Besides the bergamot lime, bergapten is a naturally occurring component of various other fruits and plants. Examples of these are figs (Ficus carica), celery (Apium graveolens), lemon oil and Queen Anne's lace (Ammi majus).[19]

Pseudoporphyria

Pseudoporphyria may occur with some medications, the most common of which is naproxen.[9,20] Other medicines associated with pseudoporphyria are nalidixic acid, tetracycline, fuorsemide, bumetanide, amiodarone, cyclosporine, pyridoxine and dapsone.[16] Frequent use of sun-tanning beds and chronic renal failure are other predisposing factors.

Pseudoporphyria is clinically characterized by increased skin fragility; erythema; and the appearance of tense bullae and erosions on sun-exposed skin, which are identical to those seen in patients with porphyria cutanea tarda. However, a clinical pearl that may prove helpful in differentiating between pseudoporphyria and porphyria cutanea tarda is that the classic features of hypertrichosis, hyperpigmentation, and sclerodermoid changes found with porphyria cutanea tarda are unusual with pseudoporphyria. The results of porphyrin studies are normal.[21]

The primary treatment of pseudoporphyria is to discontinue the offending agent whenever possible. Resolution of the clinical findings of drug-induced pseudoporphyria may take many months. Some patients may be left with permanent scarring.[21]

Lichenoid reactions

Lichenoid reactions that occur in a photodistribution are often difficult to distinguish from idiopathic lichen planus.[22] These reactions are characterized by violaceous or erythematous papules and plaques that sometimes have Wickham striae [whitish lines visible in the papules of lichen papules and other dermatoses,] Hydrochlorothiazide, hydroxychloroquine, enalapril, demeclocycline and captopril are known causes of drug-induced lichenoid reactions.

Lupus-like reactions

Drug-induced photosensitivity reactions may also include lupus-like reactions. Such reactions may resemble subacute cutaneous lupus erythematosus because of their scaling, annular, and psoriasiform characteristics.

Hydrochlorothiazide is the drug most frequently associated with this reaction but calcium channel blockers, ACE inhibitors, griseofulvin, and terbinafine are other agents that have been implicated.[23,24] The rate of reaction is low for any of these agents.

Photoaggravated tattoo reactions

Photo-aggravated tattoo reactions are most commonly caused by yellow (cadmium sulfide) tattoo pigment. Oedema and erythema may develop upon exposure to sunlight. Although the mechanism is not clear, cadmium sulfide is the light-sensitive material used in photoelectric cells; therefore, the reaction is believed to be phototoxic.

Red tattoos [red dye is mercuric sulfide (cinnabar), sienna (ferric hydrate), sandalwood, brazilwood, organic pigments (aromatic azo compounds)] have been associated with photo-aggravated tattoo reactions less frequently than yellow tattoos, and most likely, these reactions are related to the trace amounts of cadmium added to brighten the red pigment. In contrast to hypersensitivity reactions to red tattoos, reactions to pigments used to create green [chromic oxide, lead chromate, phthalocyanine dyes], blue [cobalt aluminate] and black [carbon (India ink), iron oxide, logwood] tattoos are much less common.[25]

Treatment and prognosis of photosensitivity reactions

The mainstays of treatment of drug-induced photosensitivity include identification and avoidance of the causative agent, the use of sun protection, and symptomatic relief.

Topical corticosteroids and cool compresses may alleviate drug-induced photosensitivity. In severe cases systemic corticosteroids may be utilized.

If sunscreens are not the cause of the photosensitivity, they should be used liberally. The sun protection factor (SPF) may not be a reliable indicator of protection against drug-induced photosensitivity. The SPF refers to the degree of protection against sunlight-induced sunburn, primarily that caused by UV-B. Most drug-induced photosensitivity reactions are caused by wavelengths within the UV-A range. Therefore, sunscreens that absorb UV-A should be prescribed. Sunscreens that contain avobenzone, titanium dioxide, and zinc oxide are more effective in blocking out UV-A radiation than sunscreens that contain other ingredients.[9]

In most patients, the prognosis is excellent once the offending agent is removed. However, complete resolution of the photosensitivity may take several weeks to months. Occasionally, patients may have persistent light reactivity for which the prospects for resolution may be poor.[10]

Patient Education

Patients need to be counseled regarding the possible photosensitizing properties of both prescription and nonprescription medications.

Most often, appropriate sun protection measures may prevent most drug-induced photosensitivity reactions. Some practical information on the use of sunscreens may be found in Table 3

Conclusion

All health care professionals should make an effort to educate their patients and clients and raise the awareness to photosensitivity reactions as well as necessary prevention measures. Health-care professionals should also be aware on how best to use sunscreens in an effort to prevent as much as possible the occurrence of photosensitivty reactions

References:

1. Kloog I, Haim A, Stevens R, Barchana M, Portnov B. Light at Night co-distributes with incident breast cancer but not lung cancer in the female population of Israel. Chronobiol Int.2008; 25: 65-81
2. Klinkenborg V. Our Vanishing Night. Nat Geogr. 2008;214: 102-123
3. Stevens R. Working against our endogenous circadian clock: Breast cancer and electric lighting in the modern world. Mutat. Res. 2009; 680: 106-108
4. Pauley S. Lighting for the human circadian clock: recent research indicates that lighting has become a public health issue. Med Hypotheses. 2004; 63:588-96
5. Elias SS, Patel NM, Cheigh NH. Drug-induced skin reactions. In De Piro JT et al., eds. Pharmacotherapy: A patophsyiological approach (5th Ed.). New York: Mc Graw-Hill.2002;1706-1716.
6. Koehler J. Photosensitivity. In Tisdale J, Miller D, eds. Drug-Induced Diseases: Prevention, Detection and Management. Bethesda: American Society of Health-System Pharmacists.2005; 69- 81
7. McKay M .Sun-Associated Problems. In Keystone J, Kozarsky P, Freedman D, Nothdurft H, Connor B eds. Travel Medicine 2nd Edition. New York, Mosby Elsevier.2008
8. Tisserand R, Balacs T.The Skin. In Essential Oil Safety: A guide for health care professionals. London, Churchill Livingstone.1995
9. Zhang A, Elmets C. Drug-Induced Photosensitivity. In eMedicine. 2010. Available at http://emedicine.medscape.com/. Last accessed on 20 June, 2010.
10. Allen J. Drug-induced photosensitivity. Clin Pharm. 1993;12:580-587
11. Blickers DR.Photosensitising and other reactions to light. In: Braunwald E, et al. eds. Harrison's Principles of Internal Medicine (15th ed.) New York: Mc Graw Hill. 2001; 342-348.
12. Vasssileva S, Mateev G, Parish L. Antimicrobial photosensitive reactions. Arch Intern Med.1998;158: 1993-2000
13. Rappresberger K, Honigsmann H, Ortel B, Tanew A, Konrad K, Wolff K [1989] Photosensitivity and Hyperpigmentation in amiodarone-treated patients: incodence, time course and recovery. J Invest Dermatol.1989;93: 201-209
14. Gould J, Mercurio M, Elmets C. Cutaneous photosensitivity diseases induced by exogenous agents. J Am Acad Dermatol.1995; 33:551-573
15. Heger J, Prystowsky E, Zipes D .Relationships between amiodarone dosage, drug concentrations and adverse side effects. Am Heart J.1983; 106: 931-935
16. Jafari-Fesharaki M, Scheinaman M. Adverse effects of amiodarone. PACE.1998; 21:108-120.
17. Kounis NG, Frangides C, Papadaki P et al. Dose-dependent appearance and disappearance of amiodarone-induced skin pigmentation. Clin Cardiol.1996; 19: 592-594

Practice points[7]

- Sunscreens should be applied 30 minutes before exposure for full skin exposure and should be applied thickly for maximum water-resistance
- One application is NOT enough. Experiments show a time-dependent decrease in Sun-Protection Factor [SPF] within the first few hours after sunscreen application. Swimming abd perspiration also reduce the SPF value for many sunscreens
- Sun-screen should be applied after sweating, swimming, toweling and hiking [clothing rubs it off exposed arms and legs]. Sunscreen should generally be re-applied every 40-80 minutes
- Re-applying sunscreen during the day does NOT extend the period of protection. [SPF 30 means a maximum of SPF 30 protection under ideal conditions and frequent reapplications
- The SPF is the amount of UV radiation required to cause sunburn on skin with the sunscreen on, relative to the amount required without the sunscreen. So, wearing a sunscreen with SPF 30, one's skin will not burn until it has been exposed to 30 times the amount of solar energy that would normally cause it to burn
- SPF applies to UVB rays only. It does NOT apply to UVA. An SPF 30 product with NO UVA screen will be less effective than a product with a lower SPF value which contains a UVA screen
- Sunscreens should be applied to all exposed areas of the skin, including overlooked areas such as back of the neck, tops of the feet [if in sandals] and the rims of the ears
- Multi-day exposure to sunlight increases UV sensitivity on subsequent days of exposure. Higher SPF products must be used in such cases
- DEET-containing insect repellents may decrease a product's SPF by approximately 30%. Sunscreens can increase skin absorption of DEET
- Children receive 50-80% of their lifetime exposure to UV rays by the time they are 18 years old. Sunscreens should thus be used early

18. Matheis H. Amiodarone pigmentation. Dermatologica.1997; 145: 304-318.
19. Alikhan A, Chew A, Maibach H. Berloque Dermatitis.. In eMedicine.2010. Available at http://emedicine.medscape.com/. Last accessed on 20 June, 2010
20. Günes AT, Fetil E, Ilknur T, Birgin B, Ozkan S. Naproxen-induced lichen planus: report of 55 cases. Int J Dermatol.2006;45(6):709-12.
21. Tanzi E, Da Leo V. Pseudoporphyria.2009 In eMedicine. Available at http://emedicine.medscape.com/. Last accessed on 20 June, 2010.
22. Ellgehausen P, Elsner P, Burg G. Drug-induced lichen planus. Clin Dermatol.1998;16(3):325-32
23. Reed BR, Huff JC, Jones SK, Orton PW, Lee LA, Norris DA. Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. Ann Intern Med. 1985;103(1):49-51
24. Callen JP, Hughes AP, Kulp-Shorten C. Subacute cutaneous lupus erythematosus induced or exacerbated by terbinafine: a report of 5 cases. Arch Dermatol.2001;137(9):1196-8
25. Tanzi E, Michael E. Tattoo reactions. In eMedicine.2009. Available at http://emedicine.medscape.com/. Last accessed on 20 June, 2010