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Drug and chemical induced photosensitivity from a clinical perspective

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Abstract

Drug photosensitivity is a relatively common occurrence and a range of mechanisms may be involved. Some of these mechanisms will be discussed, including the most common, that of drug phototoxicity. The potential for drug-induced photocarcinogenesis will also be covered. Different types of photosensitivity are addressed with respect to clinical presentation, mechanisms and additionally the contribution to our understanding through clinically directed investigations. Repeated controlled therapeutic use of drug phototoxicity, with psoralen-UVA (PUVA) photochemotherapy and photodynamic therapy (PDT) will also be discussed.

Introduction

Abnormal cutaneous photosensitivity describes a pathological reaction of skin to light, generally ultraviolet radiation, manifest either as a heightened erythemal (sunburning) susceptibility or reaction or as a rash occurring after sun exposure. There are a diverse range of causes of abnormal photosensitivity, which include those elicited by light alone (such as polymorphic light eruption or chronic actinic dermatitis) and those elicited by light activation of drug or chemical. Many commonly used drugs and chemicals absorb ultraviolet and/or visible radiation and

therefore have the potential to cause photosensitisation. These drugs and chemicals can be delivered exogenously through the systemic or topical route. These include prescribed and "over the counter" medications and a variety of plants, dyes, non-steroidal anti-inflammatories and sunscreens that can cause abnormal topical photocontact reactions. These drug and chemical photosensitivity reactions and the varied mechanisms involved, which are predominantly phototoxic and to a lesser extent photoallergic in nature, will be the focus of this review. Accumulation of endogenous porphyrins within the spectrum of cutaneous porphyrias and the associated abnormal photosensitivity seen with these endogenous photosensitisers will not be included within this review.

Thus, this highlights that there is immense diversity in the ways in which drug and chemical photosensitivity can present. This is in part due to the route of delivery of the agent, but in addition, the characteristics of drug, chemical and patient and the mechanisms through which the abnormal photosensitisation is caused contribute to the heterogeneity of presentation and clinical features. Much of what is discussed in relation to drug and chemical photosensitivity relates to occurrence as adverse events, which can be problematic clinically and with respect to the pharmaceutical industry and regulatory authorities. However, the repeated controlled use of drug phototoxicity in the clinical setting must not be forgotten, as with the invaluable therapies employing psoralen-UVA photosensitisation (PUVA) (1) and with photodynamic therapy (PDT) (2).

Whilst many drugs and chemicals absorb light in the ultraviolet and visible parts of the spectrum, interestingly, drug photosensitivity is not frequently documented, probably due in part to under-reporting, with affected subjects simply stopping drug if they develop an "exaggerated sunburn" or indeed attributing this to other causes, such as excessive sun exposure or a sunscreen reaction. Indeed, if it occurs in patients who are otherwise unwell and receiving polypharmacy who may not be "out and about" it may not be clinically apparent and, as such, dermatologists and primary care physicians without a particular interest in photodermatology may only rarely see cases of drug-induced photosensitivity.

Furthermore, it is very likely that idiosyncratic, probably genetic, factors come into play in determining susceptibility to drug-induced photosensitivity, at least in part and this is an evolving field of understanding. In one report by Chaabane *et al*, of 118 patients presenting with a drug-induced skin adverse effect, photosensitivity was the third commonest cause (3).

Within specialised photodiagnostic units, systemic drug-induced photosensitivity is generally reported to account for between 2-15% of photodermatoses diagnosed (4-8). In our tertiary referral photodiagnostic unit, the Scottish Photobiology Service, systemic drug photosensitivity represented 4% of the cases diagnosed during the period from 1972 to 2017, consistent with other major photodiagnostic centres and photocontact allergic dermatitis represented an additional 2% of cases. Interestingly, in one study of 229 patients with photosensitivity diseases, drug phototoxicity and phytophotodermatitis due to plant phototoxicity was

documented more commonly in Caucasians (15.9% and 6.3% respectively) than in African-Americans (0.7% and 0%), possibly indicating the protective effect of constitutive skin pigmentation against drug or chemical-induced phototoxicity (9). In contrast, significant differences were not seen for some of the other photodermatoses, such as chronic actinic dermatitis and indeed photoallergic dermatitis, indicating that constitutive pigmentation does not protect against photosensitivity of all types, including those immunologically mediated (9).

However, of course these cases only represent those actually referred for investigation of suspected photosensitivity and as such likely under-estimate the true occurrence in the population or in patient groups. For example, in one report of patients with cystic fibrosis who received ciprofloxacin, almost half reported increased sun sensitivity in a questionnaire-based study when compared with only 2.4% of a control population (10).

Action spectra

There is a degree of predictability of photosensitivity based on spectroscopic and molecular characteristics, with a drug of low molecular weight and the presence of aromatic halogen atoms being more like to be associated with a photosensitivity (11). Most photoactive drugs absorb light in the UVA region, sometimes extending into the visible part of the spectrum (mainly 315-430 nm), with the minority also sensitising in the UVB region **(Figure 1)**. This minority includes many commonly prescribed and over the counter medications, notably the thiazides, non-steroidal anti-inflammatories (NSAIDs) and quinine. In one retrospective report

of 14 patients diagnosed with drug-induced photosensitivity, monochromator phototesting showed UVA sensitivity in 10 subjects taking a range of drugs: quinine, sparfloxacin, amiodarone, doxycycline, mefenamic acid, nalidixic acid, fenbrufen, diclofenac, enalapril, diltiazem and prochlorperazine; one subject taking doxycycline was sensitive to UVA and UVB and three were tested off drug and had normal phototesting (12).

Thus, given the UVA-dependency, drug-induced photosensitivity may manifest itself at any time of the year and also may be induced by UVA and visible light transmitted through window glass. Furthermore, broad-spectrum sunscreens may be of limited benefit with respect to protection against longer wavelength UVA and visible light photosensitisation. The action spectra for induction of drug-induced photosensitivity must also be kept in mind with respect to patients receiving light-based therapies and may be problematic during UVB and UVA1 phototherapy, in terms of lowering of minimal erythema dose (MED) and of developing erythemal episodes during therapy (13-15). This is usually not an issue during PUVA as the psoralen photosensitisation typically overwhelms any lower level photosensitisation by concomitant phototoxic drugs.

Mechanisms

The varied presentations of drug-induced photosensitivity and the clinical features depend on the mechanism by which the drug has exerted its effect through from phototoxicity to the less common types of drug photosensitisation, including photoallergy and drug-induced lupus.

Overwhelmingly, drug phototoxicity is the commonest mechanism and this is a non-immunological process, which could theoretically occur in anyone given exposure to enough drug and light of the relevant wavelengths and drug and light dose-dependency may be seen. Thus, it can potentially occur on first exposure to the drug or chemical and, on stopping the drug, photosensitivity should resolve. In our experience of drug-induced photosensitivity in the Scottish Photobiology Service, approximately 90% of cases are thought to be due to a phototoxic mechanism. There are clear differences in the modes of presentation of phototoxicity and photoallergy and the clinical features may be a useful guide to the underlying process **(Table 1)**.

Whilst photosensitivity has been reported as an adverse reaction to many drugs, there are common culprits, with some of the key drugs and drug classes noted **(Table 2)**. However, interestingly, with phototoxic drugs such as quinine or thiazides, idiosyncrasy is seen, with some patients being susceptible to only very low exposure doses of drug and/or light and others being either unaffected or with only sub-clinical levels of photosensitisation. This idiosyncrasy may well be explained on genetic factors, such as polymorphisms in drug metabolising, transporter or antioxidant genes. For example, in our own work we have shown that polymorphisms in the gene for the drug metabolising enzyme and antioxidant, glutathione-S transferase M1, which is null in 50% of Caucasians, are associated with erythemal sensitivity to UVB, as assessed by MED and also in a separate study, with plasma psoralen levels and PUVA minimal phototoxic dose (MPD) and thus, at least in part, contribute to individual erythemal sensitivity to UVB and PUVA (16, 17). We have also seen an association between

polymorphisms in the melanocortin-1 receptor (MC1R) and PUVA erythemal sensitivity, as assessed by MPD (18).

Certainly, we do not invariably see drug-induced phototoxicity at high drug doses. However, given the phototoxic nature of the reaction drug dose-dependency may be observed, such as is seen with doxycycline whereby clinically manifest photosensitivity is more frequent at higher doses (19). Indeed, doxycycline phototoxicity is reported in 3% of users at a dose of 100mg daily, increasing to 20% at 150mg daily and 42% at 200mg daily (19). The characteristics of this photosensitivity have recently been comprehensively reviewed (20-22).

Interestingly, topical phototoxicity is also seen with agents applied directly to the skin such as plants, dyes, coal tar, fragrances and in particular sunscreens and topical NSAIDs, the latter being more widely used in continental Europe than in the UK.

Photoallergy to drug or chemical is much less common and indeed photoallergy to systemically delivered drugs is not well documented (23). The induction of functional photomodified Langerhans cells after exposure to fleroxacin and UVA irradiation indicates the potential for fluoroquinolone-induced photoallergy after systemic delivery in mice (23). Initial sensitisation is required and the mechanism appears to be of a type IV delayed T-cell mediated hypersensitivity reaction. It is likely that this is initiated by covalent binding of the

chromophore to skin protein and subsequent induction of the delayed T cell mediated hypersensitivity reaction. The ability of tetrachlorosalicylanilide to form photoadducts and chemical modification of human serum albumin supports this mechanism of induction of photoallergy to topically applied photoallergens (24). Thus, a photoallergic reaction should not occur on first exposure to allergen but may subsequently be triggered by only minute amounts of allergen and light exposure **(Table 1).** Topical photoallergy to sunscreens and NSAIDs is well characterised, with photopatch testing being the investigation of choice for suspected photocontact allergy **(Figure 2).**

Other less common mechanisms of drug-induced photosensitivity may be through the route of drug-induced lupus, such as with calcium antagonists, thiazides, angiotensin converting enzyme inhibitors (ACEI), beta blockers, terbinafine, NSAIDs, proton pump inhibitors, TNF alpha antagonists and cytotoxics (25-28). Other presentations are as erythema multiforme, a lichenoid reaction and pellagra (29, 30). Indeed, the same drug or drug class may induce diverse types of photosensitivity reaction in different subjects, such as photodistributed papulovesicular reactions, exaggerated erythema and lichenoid change seen in cases of fenofibrate photosensitivity (31).

Pathogenesis

The presumed mechanism for drug-induced phototoxicity is that drug or drug metabolite present within the skin, when activated by light of the relevant wavelength, acts as a

chromophore, transferring into its excited state, producing either photoproducts or photometabolites, which exert a direct substrate effect or generating oxidative damage and free radicals which, in turn, initiate end organ effects, including photohaemolysis and photosensitivity (32-34). Indeed, end organ effects may typically be of skin phototoxicity, but may also include photoallergy, photogenotoxicity and photomutagenesis, such as with the fluoroquinolones (35).

Oxidative stress may be generated via oxygen-dependent Type I and Type II photosensitisation and energy transfer mechanisms (35, 36), inducing downstream effects. These include lipid peroxidation, prostaglandin E_2 production (37) via protein kinase C and tyrosine kinase activation leading to inflammation (37) and photodegradation of nucleic acid bases, as has been shown for ciprofloxacin (33). Indeed, fluoroquinolone-induced DNA damage may occur via oxygen-dependent and -independent mechanisms involving DNA oxidation, thymine dimer formation and DNA base modification via alkylation (38) and photocleavage of DNA (39, 40). Furthermore, photoactivated naproxen has been shown *in vitro* to cause cell membrane and protein damage, lipid peroxidation and inhibition of DNA replication (34). The role of oxidative stress is emphasised by the inhibitory effect of antioxidants on drug-induced phototoxicity *in vitro* (41). The chemical structure of the molecule will influence the photochemical effects and photosensitising potential, and the fluoroquinolones are a prime example of this. Within the fluoroquinolone class, some compounds are not significantly phototoxic, such as moxifloxacin, whereas others are severely phototoxic.

The obvious effects of drug photosensitisation are manifest as skin phototoxicity. In addition, risk of ocular toxicity, particularly with drugs that photosensitise into the longer UVA and visible parts of the spectrum where retinal damage is theoretically feasible, needs to be considered. Any potential systemic toxicity is unknown but this is an area for further investigation. Furthermore, reduced efficacy of drug may also be a consideration in that photodegradation on exposure to light may result in reduced therapeutic effectiveness, constituting an adverse effect. Thus, these acute effects are to be considered in the short-term, but longer-term, pigmentation, ocular damage and potential photoageing and photocarcinogenesis need to be kept in mind and this will be discussed further.

Clinical presentation

There are many potential drug culprits, with the commoner drugs and drug classes as indicated **(Table 2)**. As most photoactive drugs maximally photosensitise to UVA wavelengths this does mean that clinical features of photosensitivity may be triggered not only by direct sunlight, but also by window glass-transmitted light, on cloudy days and by sunbeds. There are also many ways that phototoxicity can clinically manifest itself **(Table 3)**. One of the most common presentations is of an immediate prickling, burning sensation on sunlight exposure affecting photo-exposed sites (such as the face, sides and back of neck, front of chest, back of hands and extensor surfaces of the arms) **(Figure 3)** in an individual taking a phototoxic drug, and the appearance of an immediate or early onset erythema, perhaps as a solar urticaria-like presentation and sometimes a more persistent delayed erythema with pigmentation. Examples

of drugs that can present in this way include amiodarone, non-steroidal anti-inflammatory drugs (NSAIDs) such as benoxaprofen, which is no longer available, and chlorpromazine.

An exaggerated more delayed sunburn-like reaction on photo-exposed sites, with sparing of photo-protected sites, such as under the chin, upper eyelids, behind the ears (Wilkinson's triangle) and under clothing, can also be a manifestation of drug phototoxicity. For example, this can occur with quinine, thiazides or tetracyclines, notably doxycycline and demeclocycline. Some drugs produce an interesting phototoxicity in that erythema may be delayed, and the classical example of this is of the psoralens as seen both in PUVA and also with phytophotodermatitis **(Figure 4)**, where erythema is not evident until at least 24 hours after exposure and becomes more obviously manifest by 48 hours, peaking at around 72-96 hours, and subsequently tailing off and being replaced by prominent pigmentation.

The presence of a dermatitis (eczematous reaction) on photo-exposed sites in association with photoactive drug ingestion may raise the possibility of a photoallergic mechanism, although chronic repeated episodes of phototoxicity may indeed manifest as a dermatitis. In this setting other possible photosensitivity conditions, in particular chronic actinic dermatitis, should be considered in the differential diagnosis and ruled in or out based on investigation and follow up. It is unclear whether ingestion of a photoactive drug, such as a thiazide, may lower the threshold for triggering of other photosensitivity diseases, such as polymorphic light eruption.

There is no firm evidence in support or dispute of this, although based on our own experience in the Scottish Photobiology Service we certainly consider this to be a possibility.

In addition, some drugs may photosensitise not by the parent compound but through drug metabolite effect. One example of this type of presentation is that of photo-exposed site telangiectasiae caused by calcium antagonists(42, 43). This is of particular prevalence in organ transplant recipients (44) and is thought to be due to photoactive metabolites (45). As such, it may take longer than a year after discontinuation of drug for the photodistributed telangiectasiae to resolve. Hyperpigmentation may also be induced (46, 47).

Phototoxicity may manifest itself as a lichenoid reaction or as a pseudoporphyria due to basal membrane damage due to the phototoxic insult. In pseudoporphyria, the clinical presentation of photo-exposed site fragility, blistering and milia can be indistinguishable from porphyria cutanea tarda, which is the main differential diagnosis, although the porphyrin profile will be essentially normal. Examples of drugs that can cause pseudoporphyria include the propionic acid NSAIDs such as naproxen, tetracyclines, notably doxycycline, retinoids, amiodarone, sulphonylureas, furosemide and nalidixic acid (29, 48, 49). Furthermore, some photoactive drugs may even cause skin appendage damage such as photo-onycholysis, reported with many photoactive drugs, including psoralens, fluoroquinolones and doxycycline (22, 50-53). The mechanism of this is again thought to be due to phototoxic insult.

Persistent light reaction

The term persistent light reaction (PLR) was coined to describe a state of continued photosensitivity, manifest as a dermatitis after an initial episode of photocontact allergy, confirmed by positive photopatch tests, with subsequent ongoing photosensitivity even after withdrawal of the culprit topical photoallergen, typically halogenated salicylanilide or musk ambrette (54-60). The term was later encompassed within the spectrum of chronic actinic dermatitis and indeed, there is no convincing evidence in support of the PLR, with most cases retrospectively now being considered to fall within the spectrum of chronic actinic dermatitis (61, 62).

Drug culprits

Whilst large numbers of drugs and chemicals have been implicated as possible photosensitisers, in practice these should be grouped into the more commonly encountered drug categories, of which common culprits are noted **(Table 2).** Although there are many drugs reported to cause drug-induced phototoxicity, some of the more common groups or classes of drugs include the psoralens, diuretics, certain antibiotics, antifungals, antipsychotics, calcium antagonists, amiodarone, retinoids, quinine, NSAIDs and the endogenous porphyrins, which of course can also be used exogenously in photodynamic therapy (PDT) (29, 63-68), (48, 69-72). In Dundee the most commonly encountered phototoxins are thiazide diuretics, with amiodarone, NSAIDs, quinine, doxycycline and calcium antagonists also being culprits.

The thiazide diuretics appear to exert their effects often by idiosyncratic processes, and several mechanisms may be involved. Most commonly, thiazides will photosensitise via phototoxicity but thiazide-induced lupus, pseudoporphyria and a lichenoid reaction can also uncommonly occur. Due to bioavailability of drug, if drug is stopped, then photosensitivity typically resolves but may persist for 3-6 months and phototesting may be abnormal for this period (63, 73). A change to a non-photosensitising loop diuretic such as bumetanide may be advisable, as furosemide can itself induce phototoxic blistering (74). Other examples of potent phototoxins include amiodarone and chlorpromazine, both of which elicit photosensitivity through a UVA-dependent mechanism, as do thiazides, although the thiazides also photosensitise into the UVB part of the spectrum (63, 64, 75-77). On cessation of chlorpromazine there is rapid resolution of photosensitivity, whereas in contrast, with amiodarone, this can take 9-12 months for photosensitivity to resolve once treatment is discontinued. With both chlorpromazine and amiodarone it is common to encounter hyperpigmentation at sites of previous phototoxicity. Furthermore, with amiodarone, an iodoacneiform eruption may also occur on photodistributed sites.

Quinine is an idiosyncratic photosensitiser and both quinine and NSAID ingestion need to be probed for in the history as many patients will not volunteer this information regarding these drugs as prescribed or over-the-counter medications (78). The mechanism for quinine-induced photosensitivity is considered to be phototoxic, although a lichenoid pattern may also occur, and the presentation may be clinically very similar to that of thiazide or doxycycline-induced photosensitivity. Profound dyspigmentation may be a feature and vitiliginous changes

consistent with leukomelanoderma, due to temporary melanocyte dysfunction can be induced by hydrochlorothiazide (79). The action spectrum for induction of quinine photosensitivity involves both the UVA and UVB parts of the spectrum (78) and, on cessation of drug, photosensitivity can persist for 6 months or longer. The mechanism of quinine phototoxicity has been investigated and there does appear to be a fluorescent photoproduct or metabolite and possibly an intracellular target as there is no evidence of photohaemolysis (78). Whilst the calcium antagonists may uncommonly induce phototoxicity, as mentioned the more typical presentation is of photoinduced telangiectasiae, sometimes with hyperpigmentation (42, 43, 45).

The antibacterial fluoroquinolones contain a fluorine atom at position C-6 and in some of the fluoroquinolones there is also a halogen present at C-8. Photosensitivity and indeed photocarcinogenesis are well documented in pre-clinical models, with lomefloxacin, fleroxacin, ofloxacin and ciprofloxacin being reported as phototoxins (35, 80-82). Photosensitivity may be attributed to photodehalogenation, in addition to reactive oxygen species generation and energy transfer (35). Indeed 6, 8 photodehalogenation appears to be associated with increased phototoxicity, such as with lomefloxacin, fleroxacin and sparfoxacin, whereas methoxy substitution as with moxifloxacin, significantly reduces photosensitising potential (35). Indeed, lomefloxacin is considered one of the more phototoxic fluoroquinolones in humans, although several are implicated as photosensitising in the clinical setting, with occurrence rates reported at up to 3%, although possibly higher with prolonged use (35, 83-90). The action spectrum for induction of fluoroquinolone phototoxicity is the UVA region extending into the longer UVA and

visible parts of the spectrum **(Figure 1).** Interestingly, on cessation of drug, photosensitivity resolves generally within 48 hours. There is wide variation in degree of photosensitisation within the fluoroquinolone drug class ranging from being no more phototoxic than placebo control through to having a photosensitising index of >90 (63-66, 72). Interestingly, studies have also shown that certain fluoroquinolones are also photogenotoxic, photomutagenic and, in animals, photocarcinogenic with a single dose of drug and light exposure. This provides an insight into the association between drug-induced phototoxicity and photocarcinogenesis (35, 91). There is reasonable correlation between *in vitro* and *in vivo* testing and the pre-clinical studies are usually fairly informative for potential risk of photosensitivity in humans. Fluoroquinolones can additionally cause hyperpigmentation, which seems to be due to drug-melanin interaction, with impact on melanogenesis and deposition of melanin, which can persist for over a year. (63, 92-94).

Topical Photosensitisation

This can also be through the mechanisms of phototoxicity or photoallergy, and the drug and chemical classes which are associated with topical photosensitisation include diverse groups within the plants, dyes, tars, pitches and topical drugs such as phenothiazines, NSAIDs, absorbent sunscreen chemicals and porphyrins, as used in topical PDT. Whilst plants or herbal substances are rarely documented to cause photosensitivity by systemic route of delivery (95), topical photosensitivity and phototoxicity are well recorded. Topical photoallergy is less common and shall be discussed further.

Topical phototoxicity : This is exemplified by psoralen photosensitisation in phytophotodermatitis, whereby fungicidal 5-methoxypsoralen and 8-methoxypsoralen in plants and fruits and vegetables such as limes, hogweed, cow parsley and celery come into contact with skin and, in the presence of UVA, initiate psoralen-induced phototoxicity, which is usually manifest clinically as linear erythema and blistering commencing about 24-48 hours after exposure and peaking at 72-96 hours **(Figure 4).** Given that there is no defined investigation of choice, this is an important clinical picture to be aware of as it has on occasions been confused with non-accidental injury in children (96).

Topical photoallergy: Photoallergic dermatitis to topical delivery of photoallergen was initially documented in the wake of the epidemic of "soap photoallergy", attributed to photocontact allergy to halogenated salicylanilides (59, 60). These antibacterial photoallergens were later superseded by other more commonly encountered substances, namely perfumes, absorbent sunscreens agents and topically applied NSAIDs, such as the very potent phototoxin and photoallergen ketoprofen (97-105). Although photocontact allergic dermatitis is uncommon (106), it must be considered and not missed. Guidelines regarding consensus methodology for photopatch testing as the key investigation in the diagnosis and management of patients with suspected photollergic dermatitis are well established (104, 107-110). The source of photoallergen may be elusive and thus the potential for this diagnosis must be considered and photopatch testing undertaken in that setting. As examples, a topical derivative of chlorpromazine, chlorproethazine, used as a non-prescription muscle relaxant, proved to be a potent phototoxin and photoallergen (111). Additionally, occupational exposure to carprofen used for veterinary purposes was a diagnostic challenge when an outbreak of photoallergic

dermatitis was detected in a factory setting, emphasising the importance of photopatch testing as a diagnostic tool **(Figure 2).** It also emphasises the need to consider agents not necessarily included in standard batteries for photopatch testing as carprofen in fact turned out to be a potent photoallergen (112).

With potential for topical photoallergy and current exposure patterns and tonnage use, the main culprits for topical photoallergy are currently the absorbent sunscreens and NSAIDs. Sunscreens have their own history with respect to usage and photoallergy. Initially PABA and its esters were most frequently implicated, replaced by the benzophenones and to a lesser extent cinnamates and subsequently the dibenzoylmethanes (104, 107-110). In recent years, more recently introduced sunscreen chemicals, such as octocrylene, have been reported to cause topical photoallergy. This compound is a relatively frequent cause of topical photoallergic dermatitis in children, in addition to benzophenones and cinnamates (110, 113, 114). Awareness of cross-reactivity is important and often for example cross-reactions are seen between ketoprofen, octocrylene, benzophenones and fenofibrate (31, 102, 105, 110, 113).

Therapeutic use of drug photosensitisation

The use of the *Ammi majus* plant and sunlight for the treatment of vitiligo in Ancient Egyptian times was the first documentation of the therapeutic use of drug and chemical-induced phototoxicity and was the origins of PUVA therapy. Psoralens are widely used in dermatology departments in both topical and oral photochemotherapy (PUVA) and this controlled

phototoxicity can be a profoundly effective treatment for many inflammatory and chronic skin conditions such as psoriasis and eczema (1). However, high cumulative PUVA exposure does significantly increase the risk of squamous cell carcinoma of the skin (115-121). This again highlights the association between phototoxic drugs and risk of photocarcinogenesis (91).

In the context of the use of controlled phototoxicity for therapeutic purposes, the initial observation *in vitro* of drug-induced photodynamic effect was reported by Oscar Raab in 1900 when working with Von Tappeiner as a medical student undertaking studies incubating paramecia with acridine dyes for antimalarial purposes. It was observed that, in the presence of light, there was increased cell killing of paramecia, highlighting the drug-induced phototoxic effect and leading to the term "photodynamic reaction" subsequently being coined (122).

Photodynamic therapy is a process of delivering controlled phototoxicity in the presence of oxygen, generally using exogenous porphyrin-based photosensitisers. Paradoxically this can be used in the treatment of superficial non-melanoma skin cancer using fluorescent topical porphyrin precursors, in particular 5-aminolaevulinic acid and methylaminolevulinate **(Figure 5)** and red LED light irradiation (2)**.** It is also of interest that during the irradiation phase of topical PDT a prickling painful sensation is commonly experienced, consistent with that encountered with other drug photosensitisers and natural sunlight (2). Systemic PDT using systemic delivery of photosensitiser, such as Photofrin and fibre optic light delivery through a bronchoscope or

endoscope, for example in the treatment of bronchial carcinoma or other accessible solid organ tumours, can also be undertaken.

Clinical assessment

Investigations of drug-induced photosensitivity in clinical practice should always be based on an initial thorough history and examination, as clinical assessment is of paramount importance. A detailed drug history in terms of chronology of when drugs were started and stopped and the timing of dose increments is essential. Many elderly patients receiving polypharmacy also fall into the category of patients for whom other photosensitivity diagnoses, such as chronic actinic dermatitis, should be considered in the differential. As such, it is important that a full and complete evaluation is undertaken and, for any patient taking drugs with a photo-exposed site presentation, these should be considered as possible culprits.

Investigations

In terms of investigation of drug-induced photosensitivity, monochromator phototesting is the Gold Standard, and this is undertaken in tertiary specialised photodiagnostic centres (12, 123) **(Figure 6).** This involves a filtered xenon arc source to allow light to be delivered relatively monochromatically across the solar spectrum, from UVB through to UVA and into the visible part of the spectrum. Phototesting patients whilst taking potential photoactive drugs will generally show either isolated UVA sensitivity or disproportionate UVA photosensitivity

compared with UVB sensitivity and immediate abnormal urticarial reactions may be evident, in addition to abnormal delayed erythema. UVB photosensitivity may be present with some drugs such as the thiazides or quinine but is usually disproportionately not as prominent as UVA photosensitivity (12). Thus, monochromator phototesting may be invaluable in distinguishing drug-induced photosensitivity from other photosensitivity diseases, in particular chronic actinic dermatitis **(Figures 3 & 6).** In addition, involvement of the visible part of the spectrum, particularly the 400-430 nm region may occur **(Figure 1).** The preference ideally is to phototest patients "on drug" and thereafter to suggest stopping a possible culprit drug and retesting at an interval "off drug" based on understanding of the nature of the drug. For example, with fluoroquinolones retesting one week later should result in normal results, whereas with thiazides it may be an interval with of 3-6 months before improvement and resolution of photosensitivity is seen.

Some drugs may cause photosensitivity via disruption of porphyrin metabolic pathways, and drugs such as vemurafenib have been implicated in this regards (124). However, this has not been substantiated (125) and further mechanistic studies are warranted. Plasma porphyrin scan should always be undertaken in suspected drug-induced photosensitivity as the early pricking burning sensations seen with drug photosensitivity may also occur in erythropoietic protoporphyria. Furthermore, some drugs can photosensitise via drug-induced lupus, and thus ANA, ENA and histone antibodies should also be assessed.

Photopatch testing is not a reliable method for investigating topical or systemic drug-induced phototoxicity (100, 126) and the indication for photopatch testing is to investigate suspected photocontact allergy **(Figure 2),** in particular to topical absorbent sunscreens or, in continental Europe in particular, topical use of NSAIDs (104, 107-110). A European consensus is available for photopatch testing and this includes a battery of standardised absorbent sunscreen chemicals and NSAIDs agents (109, 110). The technique involves application of duplicate series of photoallegens and irradiation of one set at 24-48 h, with readings, interpretation and relevance undertaken using standard patch testing methods (104, 107-110). Interpretation may be difficult if a patient has a co-existing photosensitivity disease. However, photopatch testing should always be considered in a patient with a photoexposed site dermatitis, especially if there is a history of sunscreen or topical NSAID use or if a patient with a known photosensitivity disease deteriorates for no apparent reason (104, 110, 127). This investigation has somewhat fallen between the interests of the photobiologists and contact dermatologists and further refinement of the standardised technique is under evaluation in a current European photopatch test study.

Management

In practice, if a photosensitising drug is identified then, if possible, administration should be stopped. Photoprotection with behavioural modification, clothes, hats and appropriate broad spectrum high SPF sunscreen, including reflectant titanium dioxide if longer UVA and visible wavelengths are involved, should be used whilst on drug and after discontinuation until

photosensitivity has normalised (128). If the drug cannot be stopped, such as for example with amiodarone, UVB desensitisation may be cautiously used to induce tolerance (129).

Regulatory Requirements

Historically, knowledge of potential drug photosensitivity as an adverse effect to any new drugs coming to market was provided by anecdotal reports and post-marketing surveillance. In order for a drug to be photosensitising it must be able to absorb and initiate a photochemical reaction. Predictive information relating to new potentially photoactive drugs is important (130). Regulatory guidance (FDA and EMA) is that photosafety investigations must be undertaken for drugs that absorb between 290-700 nm and are applied systemically or topically and reach the skin or eyes (91, 131-134). In practice, many drugs fall into this category and both *in vitro* and *ex vivo* studies are indicated and subsequently controlled trials in human volunteers may be required for a potentially phototoxic drug. Molecules of low molecular weight, containing aromatic halogen atoms, with extended conjugation of double bonds and of high triplet yield are more likely to be photosensitisers (11, 134). In addition to light absorption, photodegradation, formation of singlet oxygen or superoxide anion *in vitro* should also trigger the need for photosafety testing (134). The initial investigations *in vitro* would involve establishing absorption spectra and understanding the underlying mechanisms and the molecular structure of drug and whether metabolites and photoproducts are likely. Mass spectrometry may be of use in demonstrating photodegradation, as with sparfloxacin following UVA irradiation(135, 136). Drug-induced phototoxicity should be investigated *in vitro* and

photoclastogenicity, photomutagenicity and photocarcinogenicity studies may be considered, although the International Genotoxicity Testing Working Group concluded that photogenotoxicity studies were not recommended as part of standard photosafety evaluation, based on an expert panel workshop assessment that these studies were of negligible additional value (130). Subsequently, if the *in vitro* and animal study (137, 138) signals are positive, then *in vivo* human volunteer testing should be undertaken. The *in vivo* and *ex vivo* studies may be useful as predictors but the reliability of these is not high in that often a positive signal in, for example, the 3T3 neutral red assay *in vitro*, does not necessarily indicate that a drug will be phototoxic when used clinically. The 3T3 neutral red assay is accepted as the standard pre-clinical method of *in vitro* testing for drug phototoxicity (139) and the photocomet assay for evidence of DNA damage (140). Indeed, pre-clinical in vitro non-animal phototoxicity and photoallergy testing may be employed in photosafety evaluation, with endeavours to improve specificity and sensitivity and in certain settings may minimise the need for animal and human studies (141). Photosensitivity to topical agents is often investigated in animal models of skin reactions and also in a murine local lymph node assay (LLNA) and may also be adapted for use in the investigation of the phototoxic potential of systemically delivered compounds. This appears to have supportive utility in the preclinical photosafety assessment of potentially phototoxic drugs, based on establishing a photoirritation factor, which in turn may help to triage those drugs that need to go on to testing in the human setting (139).

Healthy Volunteer Testing

Times have moved on from the volunteer testing involving sending subjects who had taken drug on a lengthy boat trip in sunny climes (63, 142). The definitive healthy volunteer study involves a combination of monochromator phototesting and polychromatic solar simulator phototesting at baseline and then on steady state of drug, and if the drug is photosensitising, to repeat the phototesting until the photosensitivity has returned to the normal range (63, 67, 84, 93, 143). An adequately powered randomised controlled double blind clinical trial format is desirable, including a positive control, such as ciprofloxacin (93), in addition to the drug under investigation. This is in order to provide reassurance of the validity of the experimental set up and to assist with blinding of assessments. The phototoxic index (PI) should be defined at each narrow waveband tested and is helpful in objectively defining the level of photosensitivity at each of the monochromator wavebands tested across the spectrum. The PI is determined based on the baseline minimal erythema dose (MED) "off drug" as a ratio of the MED at that same waveband "on drug". There is marked variation in degrees of phototoxicity between drugs within the fluoroquinolone class but, in addition, between individuals and this variation, with ciprofloxacin for example, is not explained based on skin type, and idiosyncratic genetic factors are likely to be involved (63, 67, 69). However, this robust clinical trial design in healthy volunteers, with positive and negative controls, may provide essential information on whether a drug is significantly phototoxic in humans. If this is the case then it will also provide information on wavelength-dependency and the degree of sensitivity at specific wavebands. It may also allow information on drug-induced pigmentation secondary to phototoxicity to be established. The effects of sunscreen and antihistamines may also be investigated through inclusion in the experimental design. These predictive data may provide reassurance for

regulatory purposes that a drug with positive pre-clinical phototoxicity testing is either unlikely to be phototoxic when used clinically or indeed requires caution. This is important with respect to further drug development and/or labelling and management advice for a drug with proven phototoxic risk in the clinical setting (63, 67, 69, 144, 145).

Other Effects of Drug-induced Photosensitivity

We are developing some understanding of the pigmentation that is induced by some phototoxic drugs. For example, with the tetracyclines this appears to be drug complex deposition, whereas with the fluoroquinolones, this is via melanogenesis (63, 92-94).

What is less well understood is potential systemic toxicity from photosensitising drugs. There is evidence that fluoroquinolone phototoxicity in animals can result in animal death but the role of systemic phototoxicity in humans is unclear. Furthermore, some photoactive drugs, particularly those that sensitise in the visible part of the spectrum, may carry with them unknown risk to the retina and ocular damage. This needs to be considered for any drug that photosensitises certainly to the longer UVA and visible wavelengths. Indeed, in animal model testing, histopathological analysis of the retina is advisable for drugs photosensitising to visible wavelengths (139).

Drug-induced phototoxicity and photocarcinogenesis

There is overwhelming evidence for the photocarcinogenic effects of psoralens (furocoumarins), when irradiated by UVA (PUVA) *in vitro*, in animal models and in humans, so much so that it is used as positive control for photocarcinogenesis in many pre-clinical studies (91, 115-121, 146). Monoadduct formation in the 5'6' double bond of thymidines and subsequent UVA-induced photoactivation causes DNA crosslinking and DNA repair is prevented by both these PUVA mutations and signature UVB mutations, leading to tumourigenesis (40). It is also well documented that fluoroquinolones can induce photogenotoxicty (40, 147) and phototumourigenesis in animals after systemic delivery and UVA exposure (80-82). Lomefloxacin and fleroxacin induced invasive squamous cell carcinomas in an animal model following UVA irradiation, even after a single exposure, which is of concern. Induction of cyclobutane pyrimidine dimers in double-stranded DNA by triplet-triplet energy transfer is thought to be at least one of the mechanisms implicated in the phototumourigenesis of lomefloxacin, in addition to both Type I and Type II oxidative reactions (36, 83, 148, 149).

Additionally, there is a growing body of evidence for photocarcinogenic risk of several photosensitising drugs (150-155). In a multicentre questionnaire-based case control study of 1732 patients with skin cancer (SCC, Melanoma and/or BCC) and 1550 controls, associations between ciprofloxacin or thiazide ingestion and SCC risk were documented (150).

In a separate Dutch case control study of 1318 cases and 6786 controls, the use of quinolone antibiotics and propionic acid derivative NSAIDs was associated with increased risk of

melanoma, even when used only short-term (154). Furthermore, in a large population-based case control study in Denmark, an association was seen between the use of thiazides or amiloride and risk of melanoma (151). Thus, possibly the risk of skin cancer with photosensitising drug may be greater for SCC and melanoma than BCC, although there are reports suggestive of a possible increased risk of BCC, such as with amiodarone, ciprofloxacin or tetracycline (152, 156-159).

In one population case control study in New Hampshire in >5000 subjects, an association with tetracycline use and increase risk of BCC, especially at age of <50 years was noted (153). This observation of an association between photosensitising antimicrobials and early onset BCC has been corroborated (153). In a further study, an increased incidence of both BCC and SCC was recorded in tetracycline users (152). Indeed, associations between diuretics, especially thiazides, and SCC and BCC have been reported in several studies and even short-term use of photosensitising drugs may be significant (151-153, 155, 160). It seems that the risk is most likely influenced by several factors, notably skin phototype, absorption spectrum of the drug, age of patient at time of taking the drug and duration of treatment and that the skin cancer type may also be influenced by these factors (151-153).

There are well documented reports of “exaggerated sunburn” and photo-distributed rash in patients taking voriconazole, who are usually immunosuppressed (161-164). Severe phototoxicity was reported in 8-10% of subjects (165-168) and even higher rates in patients

with cystic fibrosis (169, 170), particularly this was photosensitivity to the UVA part of the spectrum (161). The mechanism for photosensitivity is unclear and likely related to the N-oxide metabolite, which has peak absorption in the UVC and UVB, and UVB-photoproducts (165, 168, 171-173). Whilst polymorphisms in P450 CYP2C19, CYP2C9 and CYP3A4 may be implicated in the pharmacokinetics of voriconazole, there does not appear to be an identified association between phototoxicity and p450 inhibition or serum retinol levels. There is also poor correlation with drug serum levels and phototoxicity (161, 170, 174, 175).

However, the photosensitivity usually initially manifests as facial and photo-exposed site erythema, often also with cheilitis (176) and retinoid-like side effects (176). The risk may be increased by immunodeficiency, either innate or iatrogenic (168-177). A degree of suspicion of photosensitivity must be kept as misdiagnosis as cutaneous graft-versus-host disease may occur (178). Voriconazole use has also been associated with pseudoporphyria and photoaging (166, 179-182), discoid lupus erythematosus in one case (176) and with photocarcinogenesis, with both aggressive squamous cell carcinomas developing in children and adults but also with atypical lentigines and malignant melanomas (165, 183). In one report, 51 squamous cell carcinomas occurred in eight patients, including children and patients also showed facial erythema and marked photoaging, lentigines, actinic keratosis, telangiectasiae and cheilitis (180). The risk of skin malignancy with voriconazole has been identified (180, 184-186), although was not shown to be significant in one large retrospective study (177). The photocarcinogenic risk does however appear to be related to duration of therapy, certainly in

the lung transplant patient population (187), with the risk of SCC in association with chronic voriconazole ingestion rising to 28% at 5 year follow up post lung transplantation (186).

The BRAF inhibitors such as vemurafenib have also been associated with photosensitivity (188, 189) through a UVA-dependent early erythema and increased porphyrin levels (124), although this has not been consistently observed (125). In studies of patients taking vemurafenib, more than 50% have been reported to be photosensitive, and also to develop naevi, keratoacanthoma and keratinocyte proliferations, including squamous cell carcinoma of the skin. However, the mechanism of phototoxicity may be dissociated from the mechanism of keratinocyte proliferations as the latter may involve MEK inhibition and upregulation of the mitogen-activated protein kinase (MAPK) pathway (190-192).

With respect to newer drugs, pirfenidone, which is an oral anti-fibrotic, anti-inflammatory drug used for idiopathic pulmonary fibrosis, has been shown to cause phototoxicity in more than 12% of patients and is phototoxic both in cells and animals (193-197). A possible photoallergic mechanism has been proposed, but not substantiated and use of photopatch testing in the setting of investigating systemic photoallergy may result in false positive or negative reactions and is thus difficult to reliably interpret (198). This is a drug used chronically and other useful alternatives are not in abundance, and therefore management of photosensitivity is often by dose reduction and photoprotection in this otherwise ill group of patients. As a photosensitiser and immunosuppressive agent used chronically the possibility of a photocarcinogenic risk needs

to be considered, although any potential risk is unclear and studies are warranted. There are reports of photosensitivity with other newer drug groups, such as with the HIV reverse transcriptase inhibitors and with the protease inhibitors and polymerase inhibitors for hepatitis C. Any possible association between photocarcinogenesic risk and use of these chronic phototoxic drugs in immunocompromised patients must be kept in mind.

Thus, undoubtedly there is an association between phototoxicity and photocarcinogenesis with some drugs and this is proven for psoralens. There are also strong pointers to photocarcinogenesis with azathioprine. Azathioprine induces abnormal UVA photosensitivity and it is likely that the interaction between DNA containing 6-thioguanine in patients taking azathioprine, with UVA induces mutagenic oxidative DNA damage and photocarcinogenesis (199-202). This likely explains, at least in part, the marked increased risk of SCC in patients who have received organ transplants and who are immunosuppressed, particularly when regimens employing azathioprine are used (202). However, other non-photosensitising immunosuppressants, such as ciclosporin also increase skin cancer risk, notably SCC, particularly with degree and duration of immunosuppression, emphasising the role of the immune system in protecting against photocarcinogenesis (202-210).

The mechanisms for both phototoxicity and skin cancer development may not be one and the same and may be distinct. There is of course risk of skin cancer with other groups of drugs such

as the biologics, which are not photosensitising, and this may be through the mechanism of immunosuppression and immunomodulation.

There are conflicting epidemiological data available regarding risks with more chronically used photoactive drugs such as the diuretics and antimicrobials but they could well contribute to increasing lifetime risk of skin cancer. It is certainly likely that there are individual risk factors for photosensitivity and skin cancer with drugs that we do not fully understand, and whether P450s or other drug metabolising enzymes, transporters or antioxidants can be implicated in some instances should be considered. Other possible culprits are melanocortin 1 receptor (MC1R) polymorphisms, which have been shown to subtly influence PUVA erythemal sensitivity, as has the glutathione S transferase, GST M1 (16-18, 211). Patients who are null for the GST M1 gene have higher serum 8-MOP concentrations after standard oral doses of 8-MOP and lower PUVA MPDs, reflecting increased photosensitivity (17).

Conclusions

Thus, in summary, drug photosensitivity is a relatively common occurrence and a range of mechanisms may be involved and several investigations are available. Regulatory requirements are increasing and should be adhered to for any new drugs coming to market. Controlled phototoxicity is widely used therapeutically as with PUVA and PDT, for example. There remains uncertainty about the risks of chronic ingestion of photosensitising drugs and systemic, ocular or chronic photocarcinogenic risks and we need increased understanding of the

pharmacogenetics involving some of the idiosyncratic drug photosensitising reactions. A level of suspicion and vigilance, with appropriate investigations to establish a definitive diagnosis is key in the clinical setting.

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