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Shedding light on drug photosensitivity reactions

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Drug-induced photosensitivity is relatively common although under-diagnosed(1). Historically, awareness of photosensitivity as an adverse effect of a drug introduced to the market, was often only apparent at the late stage of post-marketing surveillance. This may be compounded by the marked heterogeneity in clinical presentation, individual susceptibility and diversity in drug culprits and routes of delivery. Khandpur *et al* address the subject of drug-induced photosensitivity in their concise review and speculate on possible mechanisms ranging from the role of stress through to vitamin D deficiency(2). The review eloquently highlights our current understanding of mechanisms and emphasises the fact that there is much about drug photosensitivity that we do not fully understand and that may potentially have long-lasting consequences.

Most reactions are non-immunological and phototoxic(3), and our own experience in the Scottish Photobiology Service is that approximately 90% of cases of drug-induced photosensitivity are phototoxic in nature. The majority of drugs are taken systemically and it is likely that idiosyncratic factors are operative as only a proportion of patients exposed to drug and light of the appropriate wavelengths will become photosensitive and there is marked individual variation in sensitivity(4). An insight is provided into drug photoallergy, through topical application of drug or chemical, although the mechanisms of

possible photoallergy to systemically-administered drugs are unclear. Drug-induced phototoxicity may occur with a wide range of drugs. The review details the main responsible drug groups and these include thiazides, fluoroquinolones, quinine, amiodarone and the NSAIDs.

One of the possible reasons for under-recognition of drug-induced photosensitivity is that definitive investigations are largely restricted to specialist photobiology units, as the gold standard is monochromator phototesting whilst on photoactive drug(5) . This usually reveals disproportionate UVA and sometimes visible light photosensitivity and this can help to distinguish from other photosensitivity diseases such as chronic actinic dermatitis(6). Photopatch testing is the investigation of choice for topical application of photoallergic drugs, in particular the sunscreens and NSAIDs, which are the commonest current photoallergens in Europe(7). Photopatch testing is not an investigation of choice for drugs used systemically. Some photoactive drugs may induce abnormalities in porphyrins or act through a lupus mechanism and these processes should also be excluded. Additionally, pseudoporphyria, lichenoid, telangiectatic and pellagra-like presentations may also occur.

The review touches on the area of regulatory requirements, as photoactive drugs coming to market that absorb between 290 – 700 nm do require photo-safety investigations, which initially are undertaken *in vitro*, leading on to animal studies and subsequently the mainstay *in vivo* of a randomised controlled clinical trial of monochromator phototesting on- and off-drug(5).

Khandpur *et al* stimulate most interesting thought processes regarding possible roles of antioxidant defence and the implication for NRF2 induction as a therapeutic option if the photosensitiser cannot be stopped(2). In this situation of continuing photoactive drug, such as amiodarone, UVB responses are usually normal and it is often possible to safely use UVB phototherapy to induce tolerance. This also highlights the role of MED testing as a safety measure before phototherapy in patients taking photosensitisers.

Whilst the skin is the obvious organ that is affected in drug-induced photosensitivity, what else are these drug-light interactions doing? Ocular or systemic toxicity are unknown entities and we are increasingly gathering information on the possible role of photoactive drugs in photocarcinogenesis, as exemplified by psoralens, fluoroquinolones, voriconazole and vemurafenib, and concisely reviewed by O'Gorman and Murphy(8). We are gaining insight with regards to possible links between drug-induced photosensitivity and photocarcinogenesis with drugs that are used chronically, and an open mind must be kept with respect to drugs such as fluoroquinolones, pirfenidone, amiodarone and the widely-used thiazides, in terms of skin cancer risk(9).

Drug-induced phototoxicity may also be used to therapeutic advantage in psoralen UVA (PUVA) phototchemotherapy and photodynamic therapy. It is likely that individual genetic factors determine why some patients are more susceptible to photosensitising drugs than others. In our own work we highlighted the possible role of antioxidant defence, as we showed that glutathione S-transferase (GSTM1) genotype is a determinant of PUVA photosensitivity(10). Idiosyncratic factors based on genetic polymorphisms of antioxidants and drug metabolising enzymes may well be important factors in other drug-induced photosensitivities, and should be the subject of further study.

The conclusions of Khandpur and colleagues quite rightly emphasis the need for increased awareness of the possibility of drug-induced photosensitivity. Availability of specialist investigations, notably monochromator phototesting, is invaluable in defining detailed characteristics of drug-induced photosensitivity, and in turn, facilitates understanding of possible mechanisms. Vigilance, accurate diagnosis and management are essential and for those interested in dermatological research there is an awful lot that we do not know that needs further investigation!

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