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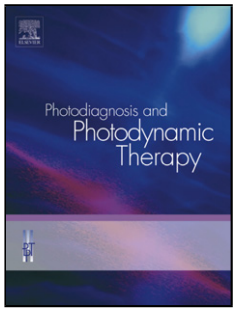

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Ultraviolet radiation exposure during daylight Photodynamic Therapy

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Highlights

- dPDT is an effective treatment for actinic keratoses (AK).
- dPDT causes minimal discomfort and is preferred by patients.
- Effective dPDT is thought to require a minimal effective PpIX weighted light dose.
- Details of the UV exposure during dPDT, highlighting the importance of sunscreens.
- Therapeutically effective dPDT can be achieved during periods of low UV exposure.

Abstract

Background: Daylight photodynamic therapy (dPDT) is an effective treatment for field-change actinic keratoses (AK), with similar efficacy to conventional PDT but lower patient pain scores. Whilst AK occur consequent to chronic solar ultraviolet (UV) exposure, paradoxically solar visible radiation is used during PDT.

Objectives: To investigate the nature and levels of UV exposure, both erythemal UV and UVA, occurring during dPDT.

Methods: Four years of solar erythemally effective UV (UVE) irradiance, UVA irradiance and illuminance data were obtained from Pubic Health England for 12 locations. For a standard 2 hour treatment period, the data were converted into standard erythemal doses (SEDs), UVA dose and protoporphyrin-IX (PpIX)-weighted dose from UVE irradiance, UVA irradiance and illuminance respectively. These three parameters were compared ascertaining the UV exposure received during dPDT.

Results: Analysis of UV exposure during dPDT showed a UK maximum average UVE exposure of 8.2 SED at Camborne (PpIX dose 23.4 Jcm^{-2}). Treatment earlier in the day reduces average UV exposure (Camborne 5.2 SED, PpIX dose 18.2 Jcm^{-2}), whilst PpIX dose achieves threshold during winter months (Camborne, November, 0.8 SED, PpIX dose 7.1 Jcm^{-2}). Cyprus and Gibraltar (with high UV exposure during dPDT) experience a maximum of 14.3 SED and 12.9 SED, with respective PpIX doses of 36.1 Jcm^{-2} and 35.1 Jcm^{-2}, in June. UVA exposure is also presented for comparison.

Conclusion: Therapeutically effective dPDT doses can be achieved at times of the day and year when UV exposure is minimal.

Keywords

Daylight Photodynamic Therapy; Photodynamic Therapy; Immunosuppression; Ultraviolet Radiation; UVA

Introduction

Daylight photodynamic therapy (dPDT) is increasingly used to treat field areas of actinic keratoses (AK) on the face and scalp and a strong evidence base exists to support its efficacy - which is equivalent to conventional PDT, with lower pain scores and high rates of patient satisfaction [1–3]. Prior to dPDT, a photosensitiser pro-drug is applied to the affected sites, it is metabolised and converted into the photosensitiser, protoporphyrin IX (PpIX). During daylight exposure, visible light activation of PpIX occurs in the presence of oxygen, leading to oxidative damage, inflammation, cell death and, ultimately, clearance of AK.

Patients are advised to undertake a minimum daylight exposure of 2 hours during treatment in the UK and elsewhere in Northern Europe, where dPDT is typically performed between April and October [4,5]. Effective dPDT is thought to require a minimum effective PpIX dose of 4 Jcm^{-2} [6], where PpIX-weighted dose is defined as the solar spectral irradiance weighted by the PpIX absorption spectrum multiplied by exposure time [7]. It is important to define the absorption spectrum used in the calculation of PpIX-weighted dose, which in our case was PpIX dimethyl ester in chloroform by Taniguchi and Lindsey [8]. The aforementioned minimum required dose and exposure times have not been firmly established and exposure times of less than 1.5 hours have not been explored [9]. Unfortunately, monitoring of PpIX-weighted dose is not routinely performed during dPDT due to the lack of a simple standardised

measurement method. Similarly, monitoring of ultraviolet (UV) exposure during dPDT is also not performed routinely.

Whilst UVB is undoubtedly a more potent carcinogen (mutating DNA forming pyrimidine dimers), UVA is also a carcinogen (damaging DNA via reactive oxygen species) and understanding the dynamics of potential UV exposure during dPDT is essential [10]. Prior to dPDT, absorbent sunscreen is applied to all exposed sites in order to reduce UV exposure during treatment, whilst aiming to only minimally impact on visible light exposure required for effective treatment.

This is important as even sub-erythemal UV exposure can induce DNA damage and cause immunosuppression, which should be avoided in patients who already have chronic UV-induced AK and in particular is relevant in the immunosuppressed patient population [10–15]. Previously, we reported on the times during the year when a dPDT threshold dose could be achieved in the UK [4]. We have now aimed to extend this methodology with UV irradiance data in order to indicate the average UV exposures that would occur during dPDT, and to investigate whether the minimum dPDT threshold dose is achievable during periods of low UV exposure.

Materials and methods

Data collection

Public Health England operates the United Kingdom's solar monitoring network [16]. They acquire erythema effective UV (UVE) irradiance, UVA irradiance and illuminance at locations throughout the UK, Republic of Ireland, Cyprus and Gibraltar. The measurement equipment consists of three sensors: a Robertson-Berger (R-B) SL-501 (Solar Light Co. Philadelphia, USA) for UVE, a SD-104Acos (Macam Photometrics, Livingston, UK) for UVA and an SD-104Lcos (Macam Photometrics, Livingston, UK) for illuminance, respectively. Measurements are performed at 1 second intervals which are archived as 5 minute averages with associated standard deviation. In this study, data from 12 locations (9 within the UK plus the Republic of Ireland, Cyprus and Gibraltar) between 2013 and 2017 were obtained and analysed for the determination of UVE exposure in SED, UVA dose and PpIX-weighted dose.

Model

PpIX-weighted dose (2 hour exposure) was calculated from measured illuminance, as described previously and verified for the UK [4]. UVE exposure in SED and UVA dose in Jcm^{-2} were calculated from the measured UVE and UVA irradiance, respectively, and integrated over a 2 hour exposure time, where 1 SED is equal to an erythemally effective radiant dose of 100 Jm^{-2}. Monthly averages of each parameter, for 2 hour time periods throughout the day, were calculated from all available data. UV exposure data (UVE dose in SED) were plotted if the corresponding PpIX-weighted dose was greater than 4 Jcm^{-2} along with UVA dose over the same periods. Data analysis was performed with a custom MATLAB (R2018, MathWorks, Massachusetts, USA) script.

Microsoft Excel 2016 (Microsoft Corporation, Washington, USA) was used to independently verify a subset of the results produced by the MATLAB program.

Results

The average UVE dose for 2 hour time intervals during each month of the year when the PpIX-weighted dose for the same period exceeded 4 Jcm^{-2} are shown in Figure 1. When the PpIX-weighted dose was below 4 Jcm^{-2}, the image is highlighted with the colour cyan to indicate periods during which it is currently thought that dPDT would be ineffective. The number of SEDs is indicated by the colour bar located to the right of each image, which is limited to a dose of 10 SEDs where anything equal to or greater than this value is displayed by the colour yellow. The time is Greenwich Mean Time (GMT), with Daylight Savings Time (DST) not considered. For Cyprus and Gibraltar, the times are set to local time, based off GMT, but do not include DST.

A geographical trend is evident in Figure 1, with locations that are more northerly located receiving lower number of SEDs than southern locations (closer to the equator). Peak average UVE exposure for locations in the UK was Camborne, with a recorded value of 8.2 SEDs. It is also evident that the PpIX dose falls below the minimal threshold value more frequently during the autumn and winter months at higher latitudes. In the summer months, in the UK, the UVE dose expressed in SED is minimised at either end of the day with the threshold PpIX-weighted dose still being achieved. For two locations in Europe (Cyprus and Gibraltar), a threshold dPDT dose can be successfully achieved all year round, although the UVE doses are very high (Cyprus maximum 14.3 SED, Gibraltar maximum 12.9 SED).

As the data are presented as a month value averaged over multiple years, there is variation within the data, which is not visible in Figure 1. For example, it is possible to have several

bright sunny days within a month which are suitable for dPDT even if all other days within that month were undesirable and, as a whole, the month did not meet the minimum dose criteria. Figure 2 shows that the average effective PpIX dose for Glasgow in November 2016 between the hours of 1300 and 1500 did not meet the minimum PpIX-weighted dose criteria. However, when the data are examined on a day-by-day basis there are 14 out of the 30 days where a minimum PpIX-weighted dose of 4 Jcm^{-2} would have been achieved.

The data presented in Figure 3 are in a similar format to those data shown in Figure 1, although show the average UVA dose, without filtering by a minimum PpIX threshold dose. In the UK, a maximum UVA dose of 25.4 Jcm^{-2} was measured in Camborne in July between 1200 and 1400. Values greater than 19.3 Jcm^{-2} were achieved across the UK throughout the summer months.

A peak UVA dose of 35.4 Jcm^{-2} was observed during June in Cyprus between the hours of 1200 and 1400 and 31.9 Jcm^{-2} in June in Gibraltar between 1300 and 1500. The UVA dose in Cyprus remained relatively high year-round with the summer months typically being greater than 15.4 Jcm^{-2} at the end of the day. It is worth noting that when DST is considered the 2 hour period at the end of the day in Cyprus would be between 1700 and 1900. Gibraltar was similar in trend, although peak doses occurred later in the day. This is due to Gibraltar's solar noon occurring later, typically 1300 local time (GMT +1).

The trends in UV data, shown in Figures 1 and 3, indicate that over the course of a year mean UV exposures (UVA and UVE) are greater during the summer months, with less within year variation seen in UVA exposures compared with the UVE exposures. The monthly UV exposure maxima occur around midday, correlating with known trends for UVA and UVE radiation [17]. Both Figures 1e and 3e display Gibraltar as having its peak UV exposure times later in the day compared with all other locations.

It should be noted that a small amount of data is not available, particularly for Cyprus and Gibraltar. Missing data is the reason for Cyprus' August appearing lower than the surrounding months in Figure 1d.

Discussion

dPDT is increasingly used to effectively treat large areas of field change actinic keratoses in both immunocompetent and immunosuppressed patients [18,19]. Treatment is extremely well tolerated and is highly effective, being comparable to more conventional hospital based PDT regimes [2,3,20]. Given that actinic keratoses arise as a consequence of chronic UV exposure

and that these patients are at high risk of skin cancer, it is understandable that patients and clinicians will have some concerns about a therapy based on daylight exposure. To date, clear explanations that dPDT requires the visible and not the UV parts of the solar spectrum for effective treatment and the generic recommendation for use of an absorbent sunscreen provide some reassurance. The importance of sunscreen application was highlighted by the very first clinical use of dPDT, where sunscreen was not applied to treatment sites resulting in increased erythema [1]. Given that patients with AK have accumulated considerable chronic UV-induced damage, the added risks of a single 2 hour exposure are likely negligible. However, in the absence of sunscreen, additional sunburn may potentially add to the discomfort of treatment. It is clear an in-depth understanding of daylight exposure and required minimum level of sun protection during treatment would better protect, inform, direct and hopefully reassure those involved in, both receipt and delivery of, this important treatment approach.

The data presented have a number of important messages: clear demonstration that protection against both erythemally weighted UV and UVA exposure is required during dPDT, with photoprotection and appropriate sunscreen use to sites exposed, in particular when treatment is undertaken in the middle of the day during the summer months. This has been recommended in UK guidelines but the data have not previously been formally evaluated in this context [21]. Although guidelines suggest the use of sunscreens of at least SPF 20 to protect patients from excess UV exposure during treatment, recent research also suggests that sunscreen application may have an adverse effect on received PpIX-dose, attenuating long wavelength UVA and visible blue light, and therefore careful selection of protection is required [22]. Our data also reinforce the message that there is enough light available for treatment to take place in the winter months. As previously stated by O'Mahoney *et al*., insufficient light level is usually not the limiting factor, it is a low ambient temperature that may adversely affect patient comfort ($<10^{o}$C) [4,23]. Diffey reported that UV index decreases after solar noon whilst temperature can remain elevated [24]. Our data also demonstrates the fall in UV exposure post solar noon but with minimum PpIX dose still achieved. It could therefore be suggested that mid to late afternoon be an appropriate time period for dPDT as the PpIX dose can be achieved, the UV exposure is lower but the temperature may remain acceptable.

Alternative approaches of treatment delivery may be appropriate, such as using light through conservatory glass, thus avoiding any restrictions of low temperatures. This would, however, require careful adjustment in time to ensure the PpIX threshold dose is met [25]. The use of daylight transmitted through glass also has the added benefit of reducing harmful UV exposure, particularly at erythemally effective wavelengths, due to the attenuating properties of glass.

However, whilst standard glass should not have significant attenuation of longer wavelength UVA and visible light, inherent or externally applied filters could impact the PpIX-weighted dose and must be taken into consideration.

To the authors knowledge, information on solar UVA dose during dPDT has not been previously reported. The importance of UVA, and whether to provide protection against it during dPDT, is unclear. UVA accounts for around 40% of the PpIX absorption spectrum and may play an active role in dPDT efficacy [22]. It has also been linked to nitric oxide production and potential cardiac benefits [26,27]. On the other hand, UVA is known to penetrate deeper into the dermis compared to UVB, initiating oxidative stress and DNA damage, again highlighting the importance of photoprotection [28,29]. Once the role of UVA is better understood the data we have provided will be available as a guide to typical exposures.

Our research provides clinicians with useful guidance with respect to the times of day that could be scheduled for effective dPDT, whilst minimising UV exposure. Particularly, this can be taken into account if treating high risk patients, such as those who are immunosuppressed or with a history of skin cancer. It is important to remember that the data presented in this study are with respect to GMT and therefore during summer months in the UK, the data relate to one hour behind local time due to DST (e.g. our data between 1200 and 1400 in June relate to a local time of 1300 to 1500).

There are limitations to the data presentation and analysis, particularly with presentation of the data as monthly averages, over a number of years, as previously described. These averages will have the largest impact on dPDT dose received, as even small variations could have disproportionally high impact if its average is around minimum effective dose. It is important to remember that regardless of the time of year, a clear sunny day will provide enough light to meet the currently regarded minimum PpIX-weighted dose. Information on the UVE dose can then be obtained from online resources.

To summarise, historical data show that daylight levels are sufficient to provide year-round dPDT in the UK. Additionally, the erythemal UV doses experienced would be high enough in the summer to induce unwanted sunburn during dPDT and thus this reinforces the need for photoprotection of exposed sites and appropriate sunscreen use. We have demonstrated that an effective dPDT light dose can be achieved during periods when UV exposure levels are low, thus potentially broadening the window for use of dPDT, which is particularly relevant in Northern latitudes, including the UK. This information may be of particular benefit when considering treatment of patients at particular risk, such as those who are immunosuppressed or have a history of skin cancer. These data provide additional important information to inform

clinicians and patients with respects to the practicalities of dPDT delivery, knowledge that will build confidence in a treatment that is inevitably based on the inherent variability in daylight exposure.

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Declaration of interest

Sally H. Ibbotson has received honoraria and travel expenses from Galderma and Spirit Healthcare. Paul O'Mahoney has received travel expenses from Galderma.

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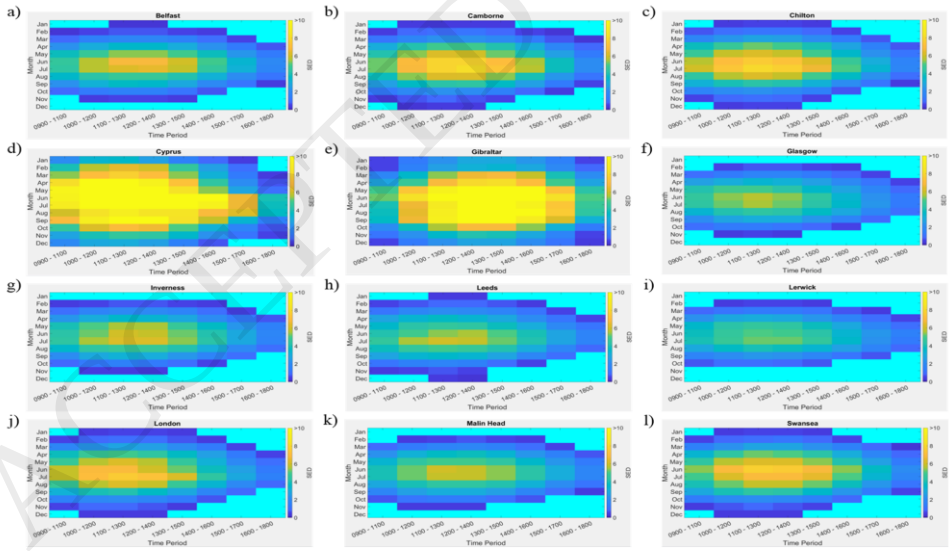
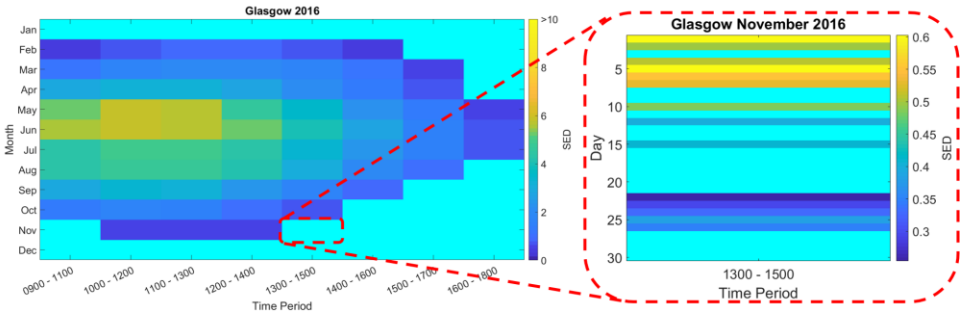
Figures Captions

Figure 1: Standard erythemal doses (SEDs) displayed in a grid format for multiple locations (each location is identified in subplot title). SED is displayed on the colour bar on the right hand side of the figure. It is limited to a value of 10 SED where values greater than or equal to this value are displayed the same (yellow). Times where the minimal effective PpIX dose is less than 4 Jcm^{-2} are blocked out and indicated by the cyan sections.

Figure 2: Glasgow 2016 data with ineffective treatment times blocked out (PpIX dose < 4Jcm^{-2}), indicated by cyan, with SED colour scale limit set to a value of 10. Inset displays a zoomed in section (showing the days of November between 1300 and 1500 hours) where treatment has been deemed inadequate and presented as cyan. November 2016 displays 14 days, out of 30, where effective treatments would be possible with low levels of UVE exposure.

Figure 3: UVA dose over the same time intervals and years as Figure 1 for each location (location in title in subplot). Note that the colour bars for locations within the British Isles have been limited to > 25 Jcm^{-2} and Cyprus and Gibraltar to > 35 Jcm^{-2}. Locations where the PpIX dose is below threshold are not omitted, as they would be the same as in Figure 1.





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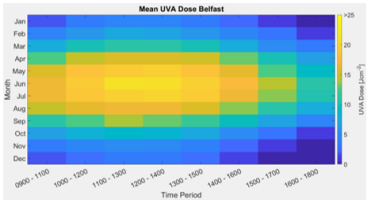
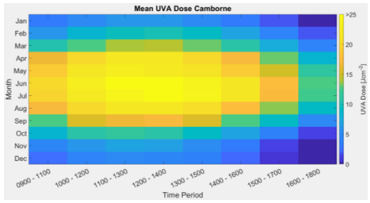


b)



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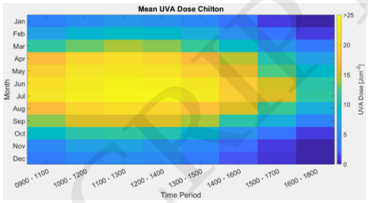

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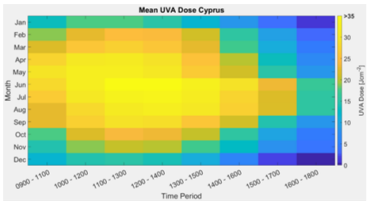

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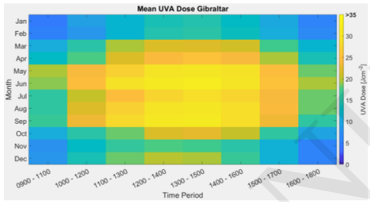

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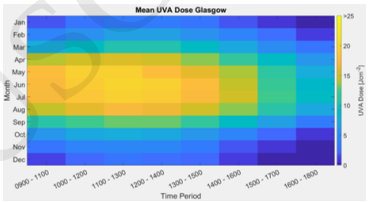

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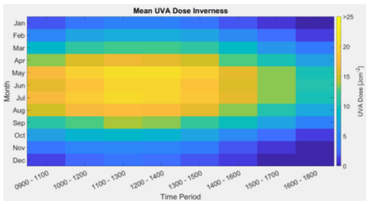

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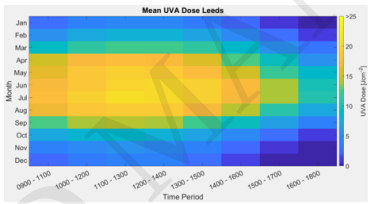

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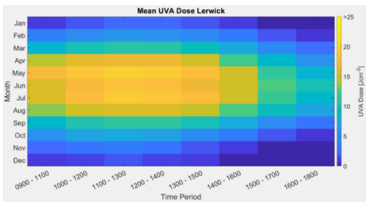

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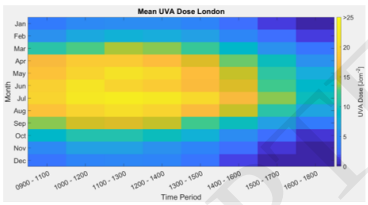

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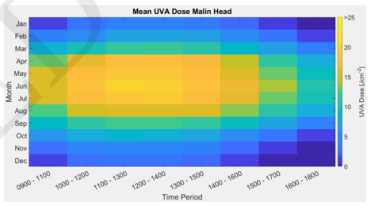

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