The use of illuminance as a guide to effective light delivery during daylight PDT in the UK

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Title: The use of illuminance as a guide to effective light delivery during daylight PDT in the UK

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What's already known about this topic?

Daylight PDT is an effective, almost painless field-treatment for actinic keratosis.

The PpIX-weighted light dose a patient receives during treatment is an important determinant of effective treatment.

Most centres undertaking daylight PDT do not objectively measure light exposure doses during treatment, and there is a lack of confidence in understanding the exposure conditions required.

What does this study add?

A new method for estimating a patient's PpIX-weighted exposure dose from a single illuminance measurement.

Detailed objective information from nine locations across the UK and Ireland with respect to possible treatment conditions for daylight PDT.

Increased understanding and confidence in the exposure conditions for effective daylight PDT in the UK.

Abstract

Background: Daylight PDT (dPDT) is an effective and nearly painless treatment for field-change actinic keratosis. Measuring the protoprophyrin-IX (PpIX)-weighted exposure dose can give an indication of when conditions are most viable for effective dPDT. It would be advantageous for practitioners if more detailed information of exposure dose and appropriate treatment conditions were available. Where sophisticated

measurement equipment is unavailable, simpler and more cost-effective methods of dose measurement are desirable.

Objectives: To devise a model whereby illuminance data can be converted into PpIX-weighted exposure dose, and to use this model to estimate appropriate times for dPDT across the UK and Ireland.

Methods: Spectral irradiance data were analysed to obtain a conversion model for illuminance to PpIX-weighted dose. This model was applied to historic illuminance data from nine sites to obtain PpIX-weighted dose across the UK and Ireland. Temperature data and an analysis of conservatory-based dPDT were also considered.

Results: A distribution of the expected PpIX-weighted dose across the nine locations is presented; however, the temperature data showed that it could be too cold for dPDT even when there is sufficient light exposure. Conservatory-based dPDT could extend the times in the year for possible treatment.

Conclusions: This proposed conversion model provides a means of using an illuminance reading to calculate the PpIX-weighted exposure dose. Dosimetry of dPDT may be carried out simply and at low cost using the presented method, however the results presented may be used as a guide for those considering dPDT, without the need to conduct measurements themselves.

Introduction

Photodynamic therapy (PDT) is an attractive treatment for superficial non-melanoma skin cancers and dysplasia, including actinic keratosis (AK). Conventional PDT (cPDT) can be performed over a relatively large surface area (up to approximately 5x10 cm^2)[1], with a high efficacy, good cosmetic outcome and high patient satisfaction[2–5]. In cPDT, light is delivered to the target area, typically using a bank of red light emitting diodes (LEDs)[1]. The dose of light delivered to the skin surface is the product of the irradiance at the skin surface and the exposure time, and sufficient photobleaching of the photosensitiser, protoprophyrin-IX (PpIX), is required for effective treatment. Both irradiance and time are easily controlled in cPDT, which allows for accurate determination of the delivered light dose. However a disadvantage of

this treatment is that it can be painful[6–8] and requires multiple visits to hospitals for patients with extensive field-change, requiring large area treatment.

A less painful and more efficient alternative to cPDT for the treatment of AK is daylight photodynamic therapy (dPDT), wherein the sun is used as the light source for treatment[6,9,10]. The sun is a broadband source containing ultraviolet, visible and infrared electromagnetic radiation which targets all of the absorption peaks of PpIX. Daylight PDT treatment times are longer than those for cPDT, with an international consensus recommending at least two hours of daylight exposure for effective treatment[11]. This exposure time can be controlled, however the irradiance of daylight at the treatment site is somewhat harder to predict, particularly in locations with variable weather conditions such as the United Kingdom. This makes accurate dosimetry of dPDT more challenging in contrast to cPDT, and is a limiting factor for physicians and patients as there is a degree of uncertainty and thus lack of confidence in treatment.

Previous studies have measured the light dose during dPDT with differing methodologies including: the use of a specialised device worn on the wrist to measure directly the PpIX-weighted light dose[10]; spectroradiometers to measure daylight spectral irradiance[12]; and handheld light meters[9]. These techniques require expensive and often bespoke equipment with associated support from a metrology specialist such as a medical physicist, while one of the advantages of dPDT itself is that it is a relatively simple treatment that does not require high specialist input. If the dosimetry associated with dPDT could be simplified so that it is cheap and simple to perform, the treatment may be more attractive where practitioners want the reassurance of accurate dosimetry but don't have the specialist support to perform some of the previously mentioned techniques. This would be particularly important in countries such as the UK, where weather conditions and light levels can vary dramatically during a day.

As a solution, we propose that illuminance, as measured in lux, can be used in a simple calculation to determine the effective PpIX-weighted irradiance, and subsequently the PpIX-weighted exposure dose. To validate this model, we compared the modelling results to direct spectral irradiance measurements made at three sites across the UK. Following validation, historical illuminance and temperature data from nine sites across the UK were analysed, and could then be used to recommend appropriate times of the year and days

for performing dPDT. This could facilitate more informed clinical practice, and provide information for centres considering dPDT as a treatment option.

Materials and Methods

Conversion Model

Data collection

Over six thousand spectral irradiance measurements of daylight were obtained from Public Health England's (PHE) monitoring station in Chilton, UK (51.575 °N, 1.318 °W), in 15 minute intervals between the hours of 09:00 and 17:00, from March to October 2015. The measurements were made in the horizontal plane using a Glacier X TE-cooled CCD array spectroradiometer (BWTek Inc, 19 SheaWay, Newark, USA), coupled to D7-SMA diffuser (Bentham Instruments Ltd, Reading, UK) by optical fibre. The instrument was calibrated in an environmentally controlled laboratory using 1000 W tungsten-halogen lamps, calibrated for spectral irradiance to the Physikalisch-Technische Bundesanstalt (PTB, Braunschweig und Berlin, https://www.ptb.de/) traceable reference standards. Full day data were excluded if there were missing time points during the day and time points were excluded if they occurred after sunset.

Model

The illuminance and the PpIX-weighted irradiance were obtained from the product of the spectral irradiance data and the luminosity[13] and the PpIX absorption[14] function respectively. A ratio of PpIX-weighted irradiance to illuminance for each data point was determined and an iterative process was undertaken to produce a model which accurately converted illuminance to PpIX-weighted irradiance. At each stage in the iterative process, results from the current model were compared to the values of PpIX-weighted irradiance derived from the measurements.

Model Verification

To test the developed model, daylight spectral irradiance data (acquired similarly to the Chilton monitoring station) from three UK sites – Salisbury (51.07 °N, 1.79 °W), Nottingham (53.07 °N, 1.24 °W) and Dundee (54.46 °N, 2.97 °W), were obtained; the model was applied to the data and the percentage difference in actual and calculated PpIX-weighted irradiances calculated. This was used as a metric to evaluate the conversion model in different locations.

Statistical Analysis

Statistical analysis was performed in JMP software, using bivariate analysis or ANOVA where appropriate. Significance is set at $p<0.01$.

UK Location analysis

Public Health England operates a solar monitoring network[15] at nine locations in the UK and Ireland (Fig. 1); illuminance is recorded using Macam Photometrics SD-104 Lcos detectors. Over half a million measurement data points were obtained at 5 minute intervals between 09:00 and 17:00 from 1st January to 31st December in 2013-15 inclusive. A custom-written MATLAB program, using the model previously described, was used to convert the illuminance values to PpIX-weighted irradiance and subsequently PpIX-weighted exposure dose. In addition, temperature data (data accessed from Weather Underground)[16] for each location were obtained over the same period as the illuminance data.

The mean daily maximal temperature and effective dose data were used to recommend months and times of the day for each location when daylight PDT could be performed. When setting the minimum criteria required for effective daylight PDT, a temperature of 10 °C and a dose of 4 J cm^{-2} were used based upon recent published literature[12,17,18]. A treatment time of two hours was assumed.

The predicted months and times of day were also calculated for conservatory dPDT, assuming no dependence on outside temperature and a reduction in the PpIX exposure dose by 25% [19].

Results

Model

Figure 2 shows the PpIX-weighted-irradiance-to-illuminance ratio as a function of the illuminance. Lower illuminance values are associated with higher ratios. As a first iteration, a logarithmic equation (Equation 1) is fitted to the data (R^2=0.34).

$$\text{Ratio} = 0.903194 - 0.03533 Ln(E_v) \quad (1)$$

where E_v is the illuminance.

The calculated PpIX-weighted irradiance (Equation 1 multiplied by the illuminance) has a mean difference of 0.53% (SD = 7.85%) when compared to the true PpIX-weighted irradiance. There is, however, a dependence of the percentage error on time of day ($p<0.01$) and year ($p<0.01$) with Equation 1 undercompensating around solar noon, and overcompensating at the start and end of the day.

The elevation angle of the sun (position of the sun in the sky) and the declination angle of the Earth (tilt of the Earth relative to the sun) (data provided by NOAA ESRL Global Monitoring Division, Boulder, Colorado, USA)[20] are used to correct for these trends (Equation 2):

$$E_e = 0.965 E_v \left(0.903194 - 0.03533 Ln(E_v)\right) \times \left((100 + \frac{3.5\phi_e}{\phi_{e(Max)}}) / 100 \right) \times \left((100 + \frac{6\phi_d}{100}) / 100 \right) \quad (2)$$

where E_e is the PpIX-weighted irradiance and E_v, Φ_e, $\Phi_{e(max)}$ and Φ_d are the illuminance, solar elevation angle, maximum solar elevation angle in the year, and the declination angle respectively.

Using Equation 2 the mean percentage difference between the calculated and the actual values is 0.04% (SD=6.80%) and the percentage error is independent of time of day or time of year.

Model verification

The model has been verified resulting in a good agreement against spectral irradiance data from Salisbury, Nottingham and Dundee. Figure 3 shows the percentage difference between the calculated PpIX-weighted irradiance and the true PpIX-weighted irradiance at three locations. The mean differences are 1.76% (SD=8.01%), -4.13% (SD=3.95%) and 2.19% (SD=4.88%) against the Nottingham, Salisbury and Dundee data respectively.

UK Location Analysis

Using the developed model, historic illuminance data from nine sites around the UK were analysed in order to present the expected mean PpIX-weighted exposure doses in each location throughout the year. Figure 4 displays the mean dose for each month over the three-year period 2013 – 2015 at each location. The mean daily maximal temperatures for each location are shown in Figure 5.

Analysis of the most appropriate treatment times of the day, following the aforementioned criteria (PpIX dose > 4 J cm^{-2} and ambient temperature > 10 °C), is given in Table 1 with full data displayed in Figure 6. Table 2 details when treatment would be possible in a conservatory - the temperature restriction of 10 °C has been removed and the dose data has been reduced by 25% to take account of the attenuation by glass[19].

Discussion

Daylight PDT is increasingly used and has a strong evidence-base to support its application in Europe and Australia[6,21]. However, the use of dPDT has somewhat lagged behind in the UK, although several centres commenced this treatment modality within the last year. There is understandable concern about the use of a treatment in the UK that relies on the weather, and guidance and confidence in the use of effective light delivery is required.

The model presented here can be used to accurately calculate the PpIX-weighted exposure dose during dPDT using only the measured illuminance, and the time and date, duration and location of treatment to

provide confidence to presubscribers of dPDT. The model first takes the illuminance reading and converts this reading in to PpIX-weighted irradiance - this is done by first accounting for the logarithmic trend of the conversion factor shown in Figure 2, and secondly by correcting for the elevation angle, which is specific to the location of measurement, and the declination angle, which is specific to the time of measurement. This process produces a corrected, accurate PpIX-weighted irradiance value, which can then be multiplied by the time of exposure to output the PpIX-weighted exposure dose.

Illuminance can be measured using inexpensive lux-meters, which makes this an attractive option in clinics where more advanced dosimetry techniques are not available. The developed model shows good accuracy in different locations (Fig. 3), which adds further confidence to the robustness of the model. This method accounts for different weather conditions, which are factored in to the error margins presented.

Deciding on the suitable months to use dPDT in different geographical locations primarily depends on the minimum PpIX-weighted exposure dose for effective treatment. There is a general consensus among several published studies which state that above a certain value there is no significant increase in treatment efficacy, ergo, there exists a minimum dose for effective treatment. However, there is no firm consensus on what this minimum dose is for effective AK treatment, with values ranging from 3-16 J cm^{-2} [9,12,17,18,22,23]. One study[10] even found no correlation between effective dose and treatment efficacy for a range of 0.2-28 J cm^{-2}. Varying reports on minimum light doses for dPDT can potentially be explained by the different measurement systems used in these studies, and the different characteristics of patients and AK lesions treated. Thinner AK lesions respond better to dPDT than thicker lesions, although there is no evidence yet to suggest that higher doses of light exposure equate to improved treatment efficacy for any grade of lesion[17].

The difference in efficacies seen between different thicknesses of AK lesions is perhaps due to the depth of penetration of the incident daylight. The peak PpIX absorption during dPDT is in the blue region of the electromagnetic spectrum where penetration depth into the skin is relatively low compared to the red portion of the spectrum where there is less absorption by PpIX, but much increased tissue penetration[24].

Therefore, it may be important to account for the nature of the lesion treated before assessing a minimum dose required. The 2012 study by Wiegell *et al.*[17] indicated that combining analysis of all AK thicknesses

could give a minimum dose whereby above a certain threshold there is no significant change in efficacy with further increasing light dose, whereas separating analysis of AK thicknesses gave no significant effects of light dose on efficacy between the individual grades of lesion. Therefore, we analysed our data against a minimum PpIX-weighted light dose of 4 J cm^{-2} based on current best estimates from the literature, and while this dose is lower than the recommendations from the European Consensus guidelines[11], it is based upon more extensive and up-to-date data from recent publications[12,17,18].

Using this value, the mean (+SD) PpIX-weighted dose each month for each location is shown in Figure 4. From these data, Table 1 was constructed showing the possible times of the year for treatment. It is worth noting that as these data encompass all weather conditions, it is likely that on clear days the expected dose would be towards or even above the one standard deviation presented in Figure 4.

Another important consideration is the ambient temperature. It is generally considered that it would not be comfortable for patients to remain outdoors in temperatures <10 °C [11]. For this reason, temperature data were included in this analysis. Data presented in Table 1 and Figure 6 show that suitable months for dPDT begin in March (London), April (Inverness, Glasgow, Malin Head, Belfast, Leeds, Swansea, Camborne) or May (Lerwick), and finish in October (Lerwick, Inverness, Glasgow and Belfast), November (Malin Head and Belfast) or December (Swansea, London and Camborne). We established that even though there may be a sufficiently high light dose in some months, the ambient temperature may be too low, becoming a limiting factor in recommending dPDT, in particular for the early months of the year. One must also consider weather conditions such as wind, where even though the ambient temperature may be above 10 °C, it may feel too cold or uncomfortable for patients to remain outdoors for extended periods of time. Therefore, even with guidelines, recommendation of dPDT should remain at the discretion of the clinician and patient.

The use of conservatories could facilitate dPDT when temperature or other weather conditions would otherwise hinder treatment if there is still enough daylight. To achieve an equivalent exposure dose to dPDT, the treatment time for conservatory-based dPDT should be increased by 33% to account for the attenuation of visible light through window glass. This would mean that, based on a recommended treatment time of two hours for dPDT, conservatory-based dPDT treatment time should be recommended

at two hours and forty minutes to maintain dose equivalence between the two methods. Studies suggest that low irradiance PDT with longer treatment times can still be as effective as conventional PDT[19,25,26]. A randomised, multicentre study found no statistical significance when comparing lesion response rate and adverse effects between patients who had dPDT for 1.5 and 2.5 hour exposures[10]. This indicates that extending the time of exposure by forty minutes for conservatory-based dPDT with a lower irradiance to maintain dose equivalence with dPDT should have little to no effect on lesion response rate or treatment tolerability.

Table 2 gave the recommended months for conservatory dPDT. These data showed that conservatory based dPDT can be recommended earlier in the year, in January (Belfast, Leeds, Swansea, London and Camborne) or February (Lerwick, Inverness, Glasgow and Malin Head), while at the end of the year the months for viable treatment conclude in October (Lerwick and Glasgow), November (Inverness, Malin Head, Belfast and Leeds) and December (Swansea, London and Camborne). These data suggest that, for south of the UK in particular, conservatory-based dPDT could be carried out for nearly the whole calendar year – in contrast to standard dPDT - owing to the higher temperatures and reduced wind effects inside the conservatory. The times in the day suitable for conservatory-based dPDT in the summer months will likely extend beyond the minimum time ranges presented in Table 2.

Tables 1 and 2 also give the time required to achieve the minimum PpIX exposure dose in the months with the highest mean dose. These data suggest that the minimum light dose can be reached in as little as 16.1 minutes in the southerly locations. It is important to note that these presented times do not serve as a recommendation for treatment times, as there are currently no studies that suggest treatment times as low as these can provide effective dPDT. In fact, it is suggested that treatment times less than one hour may provide insufficient time for photosensitiser production[27]. However, these data can give confidence to practitioners of dPDT that interruptions in the patients' daylight exposure (e.g. patchy cloud cover or rain) may be tolerable provided the recommended treatment protocol is followed.

The analysis of the most appropriate times of the day for dPDT showed suitability in the start and end months from 09:00 to either 16:00 or 17:00. Select time intervals in the 'unsuitable' months may also be appropriate for dPDT, e.g. around solar noon on clear days when there is the most daylight, even though

the mean monthly dose itself is deemed too low for effective treatment. Again, temperatures and weather effects in these periods could limit treatment. Conservatory-based dPDT slightly narrows time ranges for achieving minimum PpIX-weighted dose due to the reduction in daylight.

Conclusions

The presented data provide confidence that daylight PDT can be performed throughout the UK, from the most southerly to the most northerly locations, and that effective exposure doses can be achieved. Indeed, dPDT can be performed at times of the year in the UK not previously considered, particularly when a conservatory is used to combat the low ambient temperatures. Illuminance measurements are simple to perform and the equipment required is not expensive. The model for estimating the expected PpIX-weighted exposure dose for dPDT in the UK has been developed based on spectral irradiance measurements, and verified against spectral irradiance data from other UK locations with good agreement. It is anticipated that this model could help inform those involved in delivering dPDT clinical services, when combined with an inexpensive personal lux-meter, about patient-specific dose delivery during dPDT. Those considering dPDT may look to these results as a guide and to provide confidence without the need for conducting measurements themselves, or alternatively may carry out dosimetry using this presented method of determining PpIX-weighted exposure dose from a single measurement of illuminance.

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Table 1

		Start		End		Shortest time to achieve minimum dose	
	Latitude (°N)	Month	Time	Month	Time	Month	Time (minutes)
Lerwick	60.15	May	09:00 – 16:00	Oct	09:00 – 16:00	May	22.9
Inverness	57.48	Apr	09:00 – 16:00	Oct	09:00 – 16:00	Jul	21.4
Glasgow	55.85	Apr	09:00 – 16:00	Oct	09:00 – 16:00	Jul	21.3
Malin Head	55.35	Apr	09:00 – 16:00	Nov	09:00 – 16:00	Jun	20.4
Belfast	54.60	Apr	09:00 – 17:00	Nov	09:00 – 17:00	Jun	19.6
Leeds	53.80	Apr	09:00 – 16:00	Oct	09:00 – 16:00	Jul	19.6
Swansea	51.62	Apr	09:00 – 17:00	Dec	09:00 – 17:00	Jun	16.1
London	51.51	Mar	09:00 – 17:00	Dec	09:00 – 17:00	Jul	18.3
Camborne	50.21	Apr	09:00 – 17:00	Dec	09:00 – 17:00	Jun	16.2

Table 1: Start and end treatment months and times of the day for dPDT at each location, with respect to minimum conditions for dPDT – PpIX-weighted exposure dose >4 J cm^{-2} and ambient temperature >10 °C. These recommendations are based on a 2-hour exposure time. For the times of day presented, these represent the times in which treatment should take place, e.g. for Lerwick in May, treatment should not start earlier than 09:00 and finish no later than 16:00. Shortest times to reach the minimum PpIX exposure dose in the months with the highest mean dose are included, i.e. on average, how long will it take to receive the minimum PpIX exposure dose in the corresponding month. These minimum times are indiscriminate of weather conditions.

Table 2

Conservatory-based dPDT		Start		End		Shortest time to achieve minimum dose	
	Latitude (°N)	Month	Time	Month	Time	Month	Time (minutes)
Lerwick	60.15	Feb	09:00 – 16:00	Oct	09:00 – 16:00	May	30.5
Inverness	57.48	Feb	09:00 – 16:00	Nov	10:00 – 15:00	Jul	28.5
Glasgow	55.85	Feb	09:00 – 16:00	Oct	09:00 – 16:00	Jul	28.4
Malin Head	55.35	Feb	09:00 – 16:00	Nov	10:00 – 15:00	Jun	27.1
Belfast	54.60	Jan	10:00 – 15:00	Nov	09:00 – 15:00	Jun	26.1
Leeds	53.80	Jan	10:00 – 15:00	Nov	09:00 – 15:00	Jul	26.1
Swansea	51.62	Jan	09:00 – 15:00	Dec	10:00 – 15:00	Jun	21.4
London	51.51	Jan	09:00 – 15:00	Dec	09:00 – 15:00	Jul	24.3
Camborne	50.21	Jan	09:00 – 16:00	Dec	10:00 – 15:00	Jun	21.6

Table 2: Start and end treatment months and times of the day for conservatory-based dPDT at each location, accounting for a 25% attenuation of daylight, and negating any temperature effects. These recommendations are based on a 2.5-hour exposure time. For the times of day presented, these represent the times in which treatment should take place, e.g. for Lerwick in February, treatment should not start earlier than 09:00 and finish no later than 16:00. Shortest times to reach the minimum PpIX exposure dose in the months with the highest mean dose are included, i.e. on average, how long will it take to receive the minimum PpIX exposure dose in the corresponding month. These minimum times are indiscriminate of weather conditions.