



## Editorial

## Daylight PDT acts by continuous activation of PpIX



## 1. Introduction

During the recent 18th Congress of the European Society for Photodynamic Therapy it became clear that some confusion exists concerning the terminologies “daylight PDT”, and “PDT using artificial light sources”, and “prolonged illumination time in conventional photodynamic therapy”, and how the different modalities work. Therefore, the basic principle behind these different treatment modalities needs clarification.

“Daylight PDT” is a simple photodynamic approach used in the treatment of actinic keratoses (AK). The idea behind the treatment is to activate protoporphyrin IX (PpIX) continuously during its formation. Daylight as well as artificial light sources are similarly applicable as the treatment modalities do not rest on a specific light source but on the idea of activating PpIX during its formation, commencing the illumination at a time when no or very little PpIX has been formed [1].

## 2. Continuous activation of PpIX by daylight

Daylight was used from the very beginning to obtain continuous activation of PpIX. The term “daylight PDT” is easy to understand for the patients and, as activation of PpIX is performed outdoors it prevents the patients from crowding the clinic [2].

The continuous activation of PpIX by daylight starts 30 min after MAL/ALA application when PpIX formation begins in the skin. The continuous activation of PpIX lasts for 2 h during which no PpIX will accumulate as every time a PpIX molecule is formed it is immediately activated [3]. In each individual patient the speed of PpIX formation is very different [4]. For some the illumination time could probably be limited to 1.5 h, for others the full 2 h are necessary [2]. As we assume that the PpIX formation is independent of illumination, and as daylight PDT takes 30 min less than classic PDT (c-PDT), the total amount of activated PpIX is only about 80% of the amount activated during c-PDT. The efficacy, however, is identical [1]. By using the continuous activation approach there is no pain and inflammation is reduced [1,5,6].

## 3. Continuous activation of PpIX by artificial light sources

If artificial light sources are used the whole treatment is performed in the clinic, not contributing to simplification of the treatment. However, alternatives to daylight are needed during seasons with very low daylight intensity and when it is too cold, rainy or windy to stay outdoors for 2 h [7]. In this case it is very practical to use continuous activation of PpIX indoors by artificial light sources [8,9]. The illumination must begin when the formation of PpIX commences and acts by continuous activation of PpIX (as in daylight PDT). The term “indoor daylight” is sometimes used for this treatment modality. Many light

sources with spectra different from natural daylight can be used, however, the spectrum of light must fit at least partly to the absorption spectrum of PpIX, as no effect can be expected if light is not absorbed by PpIX [9]. The light intensity must be quite high and higher if only a minor part is absorbed in PpIX [9]. As before mentioned, different light sources have different spectra, and the speed of continuous activation varies, depending on light intensity [7,10]. The spectrum of sunlight varies during the day, during the seasons, and in different parts of the world. However, all daylight has a continuous spectrum which will always fit the absorption peaks of PpIX [7].

## 4. Classic PDT with longer illumination time

In c-PDT red diode light illumination by Actilite® for about 9 min ( $37 \text{ J/cm}^2$ ), 3 h after MAL/ALA application, will activate almost all PpIX. Approximately 80% of PpIX is activated within a few minutes, corresponding to an illumination dose of approximately  $10 \text{ J/cm}^2$ . (Fig. 1) This is probably enough to obtain full effect of PDT as it corresponds to the total PpIX amount activated in daylight PDT, ending after 2.5 h (Fig. 2). This means that more PpIX is activated than necessary for full efficacy in c-PDT [2,11]. The possibility exists that these patients are fast formers of PpIX and so may activate more PpIX over a shorter time.

Studies have been made with lower illumination intensity in c-PDT to reduce pain [12,13]. This may be done by: i) starting illumination with low intensity light after 3 h and prolonging the illumination time or, alternatively: ii) starting illumination earlier and end it as in c-PDT (Fig. 2). The speed of PpIX activation is then lower than in c-PDT where the illumination time is typically 8–10 min. (instant PpIX activation) (Fig. 2). By lower light intensity and lower activation rate pain is reduced [12,13]. In case i) the amount of activated PpIX is the same as in c-PDT when illumination starts but additional PpIX is formed during the prolonged illumination time. Both instant PpIX activation and additional continuous activation take place. The additional PpIX activation will, most probably, not result in a better cure rate [2,14,15]. In case ii) a much shorter interval of time from MAL/ALA application to start of illumination results in much less PpIX when illumination commences, and, consequently, less pain when illumination starts. In this case a combination of instant and continuous activation takes place without increasing the total amount of activated PpIX (Fig. 2).

## 5. Conclusion

The term “daylight PDT” is easy to understand but to some extent draws the attention away from the main principle of “continuous activation of PpIX”. Scientifically, it might be better to firmly establish the term “continuous activation of PpIX” and mention the light source in

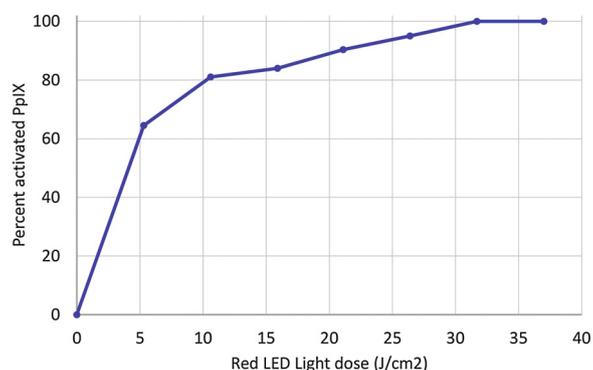


Fig. 1. shows an example of the speed of photoactivation of PpIX in classic PDT using red LED light 68 mW/cm<sup>2</sup> for about 9 min (37 J/cm<sup>2</sup>). About 80% of PpIX is activated by 10 J/cm<sup>2</sup>, 90% is activated by 20 J/cm<sup>2</sup>, and all PpIX is activated by 30 J/cm<sup>2</sup>.

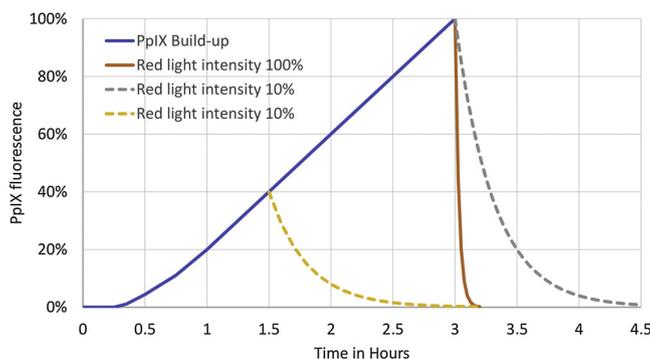


Fig. 2. shows build-up of PpIX up to 3 h after MAL application (blue line) and the normal activation phase of 9 min. If the light intensity is reduced by a factor 10 the illumination time is prolonged ten times to reach at least 37 J/cm<sup>2</sup>. The theoretical course of PpIX activation (taken from Fig. 1) is illustrated (grey line) when illumination starts after 3 h of PpIX build-up, and if illumination starts approximately 100 min (yellow line) after MAL/ALA application and ends as in c-PDT. In all cases considerable accumulation of PpIX appears before start of illumination and consequently pain will be unavoidable. As activation is slowed down, due to reduced light intensity, pain will be less during illumination. PpIX activation after 2.5 h of daylight is about 80% of the amount activated in c-PDT 3 h after application of MAL/ALA (100%).

question (daylight or the name of an indoor light source). This treatment modality should not be confused with c-PDT with prolonged illumination time.

**Conflict of interest**

The author has received speaking and travel grants from Galderma.

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