A review of pain experienced during topical photodynamic therapy—Our experience in Dundee

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KEYWORDS
Photodynamic therapy; Pain; Photосsensitiser; 5-Aminolaevulinic acid; Methyl aminolevulinate

Summary
Background: Topical photodynamic therapy (PDT) using 5-aminolaevulinic acid (ALA) and its methylated ester, methyl aminolevulinate (MAL) is widely used to treat superficial non-melanoma skin cancer (NMSC). It has been proposed that ALA PDT is more painful than MAL PDT. The aim of this paper was to compare pain scores of MAL PDT with ALA PDT in our patients and to analyse the relationship between various parameters and pain during PDT.

Methods: We retrospectively reviewed case notes and electronic records for all patients with superficial NMSC treated with PDT from June 2007 to March 2009.

Results: On univariate analysis of patients with single lesions only, we observed no association between pain and lesion diameter or pro-drug or dose or diagnosis. Pre-treatment PpIX fluorescence was significantly associated with pain. However on univariate analysis of all patients (whether single or multiple lesions) treated with PDT, MAL was associated with significantly less pain than ALA. When all the recorded variables were taken into account (multivariate analysis), diagnosis, pre-treatment PpIX fluorescence and lesion diameter were associated with pain.

Conclusions: Our data lends some support to previous published reports suggesting that the MAL PDT regime is less painful than that for ALA PDT. However, PDT pain is multifactorial and choice of photosensitiser is probably not a major pain determining factor. A prospective randomised study, with the same incubation periods for each pro-drug, is needed to definitively answer the question as to whether or not MAL PDT causes less pain than ALA PDT.

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Introduction
Topical photodynamic therapy (PDT) is effective for superficial BCC (sBCC), Bowen’s disease (BD) and non-hypertrophic actinic keratosis (AK), with high response rates and excellent cosmetic outcomes [1]. Topical PDT utilises the ability of pro-drugs: 5-aminolaevulinic acid (ALA) or methyl aminolevulinate (MAL), to stimulate the production of a photosensitiser, protoporphyrin IX (PpIX). This photosensitiser preferentially accumulates in cells with high turnover, which explains the relative tumour specificity of PDT. Subsequent illumination of PpIX-enriched tissue leads to the production of singlet oxygen and free radicals, which induce tumour necrosis.

We have almost 15 years experience in the use of topical PDT for NMSC and other skin diseases. Over this period, we have undertaken over 5000 PDT treatments. We initially routinely used ALA for more than 10 years and introduced the use of MAL in June 2007.
MAL is currently the only licensed photosensitiser pro-drug for topical PDT in the UK and is the methyl ester of ALA. It has been proposed that because of the enhanced lipophilicity [2], MAL can penetrate more easily into cells than ALA and may lead to more effective PDT. Pain is currently the main limiting factor for cutaneous PDT. The number of patients reporting significant pain and having to stop treatment because of this, varies considerably [3–5]. It is of interest that Kasche et al. reported that 54% of patients undergoing ALA PDT for AKs located on the scalp, had to stop treatment because of pain [4]. However, the exact mechanism of PDT-induced pain is unclear. Maximal pain usually occurs in the early part of irradiation during PDT and then gradually reduces [6,7]. A number of reports suggest that MAL PDT is less painful than ALA PDT [4,8–10]. However, pain associated with PDT is often reported to be multifactorial and there are a number of other studies, which have not found a difference between pain induced by either ALA or MAL PDT [11–15]. We reviewed pain experienced by our patients during MAL PDT and compared this with similar data from a cohort of patients treated with ALA PDT over the same period.

Aim

The primary aim of this paper was to compare pain scores of MAL PDT with ALA PDT. The secondary aim was to analyse the relationship between various parameters with pain during PDT.

Methods

We retrospectively reviewed case notes and electronic records for all patients with superficial NMSC (AK, BD and sBCC) treated with MAL from June 2007 to March 2009. Patients treated for other diagnoses were excluded to avoid confounding of results. Patients were identified from the in-house PDT database. All patients treated with ALA PDT within the same time period were included in the ALA cohort. Data collected included diagnosis, lesion size, pre-treatment PpIX fluorescence intensity and pain scores. When patients had multiple lesions the mean scores for the different parameters, were used for analysis i.e. data was analysed per patient rather than per lesion as it was considered that pain scores were more likely to reflect patient characteristics than lesion characteristics. For lesions receiving multiple treatments, VAS scores for the first treatment only were analysed.

Our departmental PDT treatment protocol involves application of pro-drug (Metvix cream® , Galderma, UK or 5-aminolaevulinic acid, 20% (w/v) in oil in water base, Manmed Pharmaceuticals, UK), for either three (MAL), four (AK & BD) or six (sBCC) hours (ALA), to lesions prepared by gentle abrasion (with a spatula or curette) without local anaesthetic. Visual fluorescence of the lesion was assessed using a Wood’s lamp and graded on a four-point scale for intensity (none, mild, moderate, strong). All patients were routinely offered cooled air treatment (Cynosure®) during irradiation. Irradiation was performed using one of several light sources available in the department [5]. The Aktlite® LED source was used for MAL PDT but we also used either the 630 nm diode laser (Diomed®) or the PDT1200 for ALA PDT. Initially MAL PDT was used at an irradiation dose of 37 J/cm², as per manufacturer recommendations. However, our early impression was that response to a single treatment cycle with MAL PDT amongst our patients was lower than expected and we therefore increased the dose to 75 J/cm². ALA PDT treated lesions were irradiated with a standard dose of 125 J/cm² for laser and non-LED sources or 75 J/cm² if using LED sources. The treatment cycle as above was repeated at one week for BD and sBCC. All patients routinely scored pain on a visual analogue scale (VAS) immediately after treatment.

Pain scores in the ALA and MAL groups followed an approximately normal distribution with similar variances. Pain in these pro-drug groups was compared by examination of graphs and use of the Student t test. Associated methods were used to construct confidence intervals (CIs).

To explore factors that might influence pain, a least squares linear regression model was constructed. The association between pain and each recorded variable was explored by both univariate and multivariate analysis. However to avoid confounding results we excluded patients with multiple lesions from this analysis. A p-value of ≤0.05 was regarded as ‘significant’.

Results

A total of 54 patients (77 lesions) treated with MAL PDT were identified from the PDT database. Twelve of these patients received PDT to more than one lesion. Over the same period 52 patients (95 lesions) were treated with ALA PDT of whom 20 had more than one lesion treated. The majority (91%) of lesions treated with MAL PDT were sBCC and BD whilst the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate analysis (corrected regression coefficient)</th>
<th>Univariate analysis (crude regression coefficient)</th>
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<tbody>
<tr>
<td></td>
<td>Coefficient (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Pro-drug (ALA vs. MAL)</td>
<td>−1.204 (−2.598 to .189)</td>
<td>0.089</td>
</tr>
<tr>
<td>Fluorescence (graded as 0–3)</td>
<td>.958 (.377 to 1.539)</td>
<td>0.002</td>
</tr>
<tr>
<td>Lesion diameter (cm)</td>
<td>.218 (.041 to .394)</td>
<td>0.016</td>
</tr>
<tr>
<td>Diagnosis (BD, sBCC, AK)</td>
<td>−.977 (−1.724 to −.229)</td>
<td>0.011</td>
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<tr>
<td>Dose (J/cm²)</td>
<td>−.012 (−.034 to .009)</td>
<td>0.264</td>
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</table>

* Total patients with single lesions = 71. However one patient had to be excluded due to incomplete data in case-notes.
Table 2  Parameters that might potentially predict PDT pain.

<table>
<thead>
<tr>
<th>Non-modifiable factors</th>
<th>Modifiable factors</th>
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<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td><strong>Treatment protocols</strong></td>
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<tr>
<td>Age: None of the studies published have found a significant relation between age and pain [3,10,13,14,17,18,21].</td>
<td><em>Light source (i.e. influence of wavelength):</em> Conflicting data have been published regarding the benefit of red vs. green light irradiation [24,25]. Two studies have reported no difference in pain scores between broadband and LED light sources [5,26]. Interestingly variable pulsed light delivery seems to be less painful than a continuous LED light source [30].</td>
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<td>Sex (male): Only two studies have suggested an association between male sex and pain [3,14]. However multivariate regression analysis correcting for all confounding factors was not performed. A number of other studies have not supported this association [10,13,18,21].</td>
<td><em>Fluence:</em> Ericson et al. reported that low fluences are associated with lower pain scores [6] and suggested that there is no increase in photobleaching (and hence efficacy) beyond 40 J/cm². Two further studies do not support this association [3,7], which might certainly be a threshold effect as it is well known that the majority of PDT pain is experienced within the first few minutes of irradiation.</td>
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<td>Genetic, ethnic &amp; cultural factors: No studies have looked at these so far.</td>
<td><em>Low fluence rate:</em> A number of studies have suggested significant (clinically relevant) reduction in pain scores when employing low fluence rates [5,17,19,23,27–29]. However, Ericson et al. [6] did not observe this association when comparing 30 mW/cm² vs. 75 mW/cm². Moreover as with fluence, there might be a threshold effect and one might not observe a significant association beyond a certain threshold fluence rate (possibly of the order of 10–15 mW/cm²).</td>
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<td>Skin phototype: Lower skin phototypes have been shown to be associated with more pain in two studies [13,21]. However, three other studies do not support this association [3,14,18].</td>
<td><em>Photosensitiser (ALA/MAL):</em> A few studies have suggested that MAL is less painful than ALA [4,8–10]. However, the association might not hold true when other confounding factors are taken into account and at least four other studies do not support this association [11–14].</td>
</tr>
<tr>
<td>Chronic use of oral analgesics: No association reported [13].</td>
<td><em>Duration of application of photosensitiser:</em> None of the studies so far have been designed to study the effect of this on pain.</td>
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<th><strong>Lesion characteristics</strong></th>
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<tr>
<td><strong>Diagnosis:</strong> Two studies suggested that AK was associated with more PDT-induced pain than other NMSC [3,21]. However multivariate analysis correcting for all other confounding factors was not performed. Our data suggest that PDT-induced pain with BD &gt; sBCC &gt; AK.</td>
<td>1st vs. 2nd treatment (probably a non-modifiable factor): Virgili et al. found no difference in pain scores between 1st and 2nd treatments [21], whilst three further studies reported conflicting data [10,17,22].</td>
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<td><strong>Size:</strong> Two studies, apart from our present review, have suggested that larger lesions might be associated with more pain during PDT [3,18]. However confounding variables were not corrected for. Two further studies did not support this association [13,17].</td>
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<td><strong>Body site:</strong> Three studies have suggested that lesions on head and neck are more painful than lesions at non-head and neck sites [3,14,21]. However confounding variables were not accounted for. Two studies found no effect of lesion location when other factors were accounted for [13,17].</td>
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<td><strong>Erythema of lesions:</strong> Only two studies have looked at this so far with one finding no relation [22] and the other suggesting a relation between pre-treatment erythema and pain. However correction for PpIX fluorescence or body site was not performed [18].</td>
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<td><strong>Pre-treatment fluorescence:</strong> Only one study apart from our case series, observed a positive correlation relation between PpIX fluorescence and pain on multivariate analysis [17]. Three other studies did not support this observation [3,6,23].</td>
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majority (84%) of lesions treated with ALA PDT were BD and AK. This difference reflects our departmental use of MAL PDT for its licensed indication and ALA PDT for field change AK.

The mean VAS score for patients treated with MAL PDT [5.07; standard deviation (SD) = 2.06, range = 0.5—9] was lower (p = 0.01; difference between means = 0.97 cm, 95% confidence interval = 0.24—1.72 cm) than that for patients treated with ALA PDT (6.04; SD = 1.74, range = 2—10). The median lesion diameter for lesions treated with MAL PDT (2 cm; range = 0.5—10; inter-quartile range = 1.5—3 cm) was lower (p = 0.037, 95% confidence interval for difference in medians = −1.8—0) than that of lesions treated with ALA PDT (3 cm; range = 1—16; inter-quartile range = 1.5—8.05). This could have accounted for difference in pain scores observed between the pro-drug groups. When we analysed pain scores from patients treated with single lesions only, the difference in pain scores between the MAL and ALA groups did not reach statistical significance on univariate analysis (Table 1). Taking other recorded variables (including lesion diameter) into account (multivariate analysis) there was a suggestion of more of an association between pro-drug group and pain, but this was not significant.

Of the variables we could include on univariate analysis, only pre-treatment PpIX fluorescence was significantly associated with pain. We observed no association between pain and lesion diameter or pro-drug or dose or diagnosis. However, when all the recorded variables were taken into account (multivariate analysis), diagnosis (pain for BD greater than for sBCC greater than for AK), pre-treatment PpIX fluorescence and lesion diameter were associated with pain (Table 1).

Discussion

In keeping with previous studies [4,8—10], our survey findings when analysing all patients’ data, whether they had one or more lesions treated, supported the suggestion that MAL PDT is associated with less (albeit a small difference of 0.97 cm on the VAS scale) pain than ALA PDT, with these conventionally used regimes. This suggestion observed in previous studies has been a factor in clinicians choosing MAL in preference to ALA for cutaneous PDT. However most of these studies, like our survey, used different treatment protocols for MAL and ALA, which might explain the differences in pain observed. Moreover, it is important to note that the median diameter of MAL PDT treated lesions in our series was significantly lower than that of lesions treated with ALA PDT, which might have influenced pain scores. The association did not reach significance when we excluded patients with multiple lesions, even when other factors were corrected for (Table 1). In virtually all published studies (including our cohort) reported differences in pain scores were of a magnitude often less than 10—15%, which might not be a difference clinically perceptible by patients. Most previous studies assessed MAL PDT with shorter MAL incubation periods than for ALA [4,8]. This would be appropriate if there was evidence that ALA needed to be applied longer to achieve the same efficacy. There is no such evidence. The three studies that employed identical incubation times for ALA and MAL for the treatment of NMSC did not detect any differences in pain scores between the pro-drugs [11,12,14].

Various factors influence PDT-induced pain (Table 2). None of these factors has consistently been reported across all studies to be associated with PDT pain. So, although evaluation of patient and lesion characteristics (Table 2) is interesting, it is not yet clinically very helpful as these are non-modifiable factors and can only be used for predictive (pain) purposes to tailor analgesia to the patient.

The mechanism of PDT pain has yet to be completely elucidated. However, a number of mechanisms for PDT pain have been proposed including stimulation of free nerve endings, by hypoxia or by singlet oxygen itself, produced during irradiation [16]. Consequently it is conceivable that any process that increases the rate of tissue hypoxia and or singlet oxygen generation would increase the amount of pain experienced during PDT. Mikolajewska et al. used the rate of PpIX photobleaching as a surrogate marker of these factors and showed that the time for pain induction was proportional to the rate of PpIX photobleaching (for either MAL or ALA) [16]. They also demonstrated in normal skin that ALA induced three times more PpIX than MAL (although they were not able to demonstrate a significant relation between PpIX fluorescence and pain), which might explain the apparent difference in pain scores. However, if the rate of photobleaching of ALA or MAL can be reduced, the influence of photosensitiser on pain should theoretically be minimised. PDT at low fluence rates (which should consequently reduce the rate of tissue hypoxia) has been shown to be consistently associated with low pain scores [19,20] and this approach is promising for the future of PDT. Low fluence PDT is probably the single most influential modifiable factor that can be used to reduce PDT pain. None of the studies to date have shown a clinically significant reduction in pain scores after adjustment of the other treatment parameters (Table 2). Evaluation of patient and lesion characteristics (Table 2) though interesting, is clinically not very helpful as these are non-modifiable factors and can only be used for predictive (pain) purposes to tailor analgesia to the patient.

There is a need for more work to determine the most appropriate techniques to reduce PDT-induced pain when it occurs. If it is possible to prevent (or reduce the severity of) pain by choice of pro-drug that would be helpful. A prospective randomised study, with the same incubation periods for each pro-drug, is needed to definitively answer the question as to whether or not MAL PDT causes less pain than ALA PDT.

References


Topical photodynamic therapy