In-vivo singlet oxygen dosimetry of clinical 5-aminolevulinic acid photodynamic therapy


Abstract. Photodynamic therapy (PDT) is a viable treatment option for a wide range of applications, including oncology, dermatology, and ophthalmology. Singlet oxygen is believed to play a key role in the efficacy of PDT, and on-line monitoring of singlet oxygen during PDT could provide a methodology to establish and customize the treatment dose clinically. This work is the first report of monitoring singlet oxygen luminescence in vivo in human subjects during PDT, demonstrating the correlation of singlet oxygen levels during PDT with the post-PDT photobiological response.

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The photobiological response to the $I_{\text{long}}$ treatment sites were more pronounced and more clinically significant compared to $I_{\text{short}}$ treatment sites (Fig. 1). Consistent with Ref. 9, edema and erythema response peaked at 15 min and 24 h following PDT, respectively. Subsequent analysis was performed using the maximal photobiological skin response: acute edema at 15-min post-PDT and erythema at follow-up 24-h post-PDT. PS-induced $^{1}$O$_{2}$ signal was defined by change in $^{1}$O$_{2}$ luminescence between pre-ALA (time of minimum PpIX concentration) and pre-PDT (time of maximum PpIX concentration) time points.

Several researchers have shown that the degree of erythema and edema following ALA-PDT is predictive of clinical outcome in various dermatologic conditions. To evaluate the relationship between $^{1}$O$_{2}$ signal and photobiological skin responses (edema and erythema), we applied repeated-measures linear mixed model analysis. Using this model, the $^{1}$O$_{2}$ luminescence signal significantly correlated with acute edema in $I_{\text{long}}$ sites ($P=0.01$) and 24-h follow-up erythema for $I_{\text{long}}$ and $I_{\text{short}}$ combined ($P=0.028$) (Table 1).

### Table 1: Effect of $^{1}$O$_{2}$ signal on photobiological responses based on a linear mixed model regression analysis of the data.

<table>
<thead>
<tr>
<th>$^{1}$O$_{2}$ Signal</th>
<th>Edema$^{*}$</th>
<th>Erythema$^{*}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope (95% CI)</td>
<td>$P$ value</td>
</tr>
<tr>
<td>Slope test†</td>
<td>0.009 (ST)</td>
<td>0.527</td>
</tr>
<tr>
<td>$I_{\text{short}}$ sites only</td>
<td>-0.002 (-0.015, 0.011)</td>
<td>0.747</td>
</tr>
<tr>
<td>$I_{\text{long}}$ sites only</td>
<td>0.035 (0.011, 0.059)</td>
<td>0.010 (ST)</td>
</tr>
<tr>
<td>Combined sites</td>
<td>0.017 (0.002, 0.031)</td>
<td>0.028 (ST)</td>
</tr>
</tbody>
</table>
could be modeled to describe this correlation. The relationship between erythema and $^{1}O_2$ signal showed no significant difference in slopes between $I_{\text{short}}$ and $I_{\text{long}}$ sites ($P=0.527$). As a result, correlation between follow-up erythema and $^{1}O_2$ signal was investigated with a common slope fitted to the combined dataset for the $I_{\text{short}}$ and $I_{\text{long}}$ sites (Fig. 2). The interpretation is that the percent change in $^{1}O_2$ signal from baseline is positively correlated for both sites in a similar way, and thus can be described using a common slope.

On the other hand, the correlation between acute edema and $^{1}O_2$ signal was modeled separately for $I_{\text{short}}$ and $I_{\text{long}}$ sites because they had unequal slopes ($P=0.009$) (Fig. 2). In fact, greater edema was significantly correlated with greater percent change from baseline in $^{1}O_2$ signal but only for the $I_{\text{long}}$ sites ($P=0.01$), not $I_{\text{short}}$ sites ($P=0.747$) (Table 1). Interestingly, only $I_{\text{long}}$ sites showed a significant correlation between $^{1}O_2$ signal and acute edema (Fig. 2). It is possible that the minor acute edema at the $I_{\text{short}}$ sites (median score of 0.25 out of 10) may not have been clearly discernable by the blinded investigators in a 2-D photograph, and thus may not have correlated significantly with the quantitative $^{1}O_2$ signal.

Unexpectedly, a decrease in $^{1}O_2$ signal after the incubation period was observed in some treatment sites. This might be related to modification of skin optical properties by ALA and its carrier. A carrier-only control treatment site could potentially provide additional information when incorporated in future studies.

This is the first study showing the feasibility of monitoring PS-generated $^{1}O_2$ signal in vivo in human subjects. $^{1}O_2$ signal measured immediately prior to PDT light irradiation correlated significantly with the photobiological response to ALA-PDT in normal skin. As a result, monitoring $^{1}O_2$ production in the skin is predictive of the clinical ALA-PDT outcome and is a helpful tool for customizing the clinical ALA-PDT treatment.

Acknowledgments

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References