Pilot study to determine the efficacy of ALA-PDT photorejuvenation for the treatment of facial ageing

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Abstract

Objective. The study was divided into two parts. The objective of the preliminary study was to evaluate the optimum dose and tolerance of 5-aminolaevulinic acid (5-ALA) compared to a placebo cream with a 633-nm LED light in normal, healthy, volunteer forearm skin. The second study was to establish if ALA-PDT treatments improve the signs of ageing.

Results. Threshold photosensitization was observed using 5% 5-ALA under plastic occlusion for 30 minutes following a dose response study of forearm skin. Mild improvement was observed, using this concentration and time, for periorbital skin aging. Other anecdotal positive results of photorejuvenation are reported for facial and chest areas.

Introduction

Photodynamic therapy (PDT) for cancer patients has developed into an important new clinical treatment modality over the past 25 years. PDT involves administration of a tumour-localizing photosensitizer or photosensitizer pro-drug (such as 5-aminolevulinic acid (5-ALA), a metabolic precursor of protoporphyrin IX in the haem biosynthetic pathway) and the subsequent activation of the photosensitizer by light. Although several photosensitizers other than 5-ALA-derived protoporphyrin IX (PpIX) have been used in recent years, most recent research activity has been focused on 5-ALA-PDT

Photodynamic therapy is increasingly used to manage non-melanoma skin cancers including some superficial basal cell cancers, Bowen’s disease and actinic keratoses (1). PDT is a non-invasive tissue sparing modality with reported good cosmesis with preservation of connective tissue promoting reduced scarring potential (1).

Exogenous 5-ALA increases the intracellular production of the endogenous photosensitizer PpIX, via the haem pathway, with preferential accumulation in neoplastic tissue (2). Rodriguez demonstrated that ALA-PDT was an effective treatment for both photorejuvenation and actinic keratosis (3).

Evidence suggests a variety of mechanisms responsible for the photostimulatory effects of light. It is well documented that visible light energy is absorbed by mitochondria (4), causing a chain of molecular events leading to an increase in cell energy and activation of nucleic acid synthesis. Light therapy stimulates low levels of phototoxic activity (the production of cytotoxic singlet oxygen) leading to increased levels of cellular activity and release of prostaglandins, cytokines and growth factors. These products lead to the stimulation of dermal fibroblasts and keratinocytes that produce collagen and elastin (5,6), helping reduce the signs of ageing. This therapy relies on specific patterns of light exposure to trigger new collagen production without thermal tissue damage.

Patients and methods

Subjects

Six subjects were recruited with normal forearm volar aspect skin and all displaying facial photodamage grade II (Glogau scale). For this study, subjects had no inflammatory skin conditions in the test areas, had no previous problems with photosensitivity or were prescribed photosensitive drugs.
A light source comprising a hinged planar array of light emitting diodes was used for this study. Patients received all their treatments from an LED light source emitting at 633 nm with an optimized dose of 126 J/cm² and intensity of 105 mW/cm² (Omnilux revive, Photo Therapeutics Ltd, Altrincham, Manchester, UK).

**Treatment**

**Preliminary dose ranging study—volar forearm skin.** Skin was prepared by a single pass stratum corneum tape stripping (Micropore, 3M) and isopropyl alcohol/acetone degreasing. Three concentrations of 5-ALA (5%, 10% and 20%) in Unguentum Merck, or “placebo” cream (Unguentum Merck) were applied to the forearm. The test area was then occluded using light occluding blue gauze for between 30 and 120 minutes. After the appropriate contact times the gauze and tegaderm were removed, excess cream was wiped away and the test areas exposed to Omnilux revive for 20 minutes. The unit was positioned approximately 5 cm from the test area for the duration of the treatment.

**Secondary pilot study—lateral periorbital skin.** Skin immediately around the periorbital region was prepared by stratum corneum single pass tape stripping (Micropore, 3M). A 5% concentration of 5-ALA in Unguentum M, was applied to the test area and light occluded using tegaderm and blue gauze for 30 minutes. After the appropriate contact times the gauze and tegaderm were removed, excess cream was wiped away and the test areas exposed to Omnilux revive for 20 minutes. The unit was positioned approximately 5 cm from the test area for the duration of the treatment.

**Assessment**

**Preliminary dose ranging study.** Baseline assessments of the test area were recorded. Assessments of erythema, oedema, and pigmentation were recorded immediately post exposure to light and on days 1, 2, 3 and 7. At each assessment the subject’s opinion of the treatment tolerance was recorded.

**Secondary pilot study.** Baseline assessments of the test area were recorded. Assessments of pain, erythema, ulceration, blistering and pigmentation were recorded using a scale of 1–10 immediately post exposure to light and on days 1, 2, 3 and 7. At each assessment the subject’s opinion of the treatment tolerance was recorded.

Digital photography (Canfield) was used to record changes in the test area, two exposures per periorbital region (eyes open and closed), and two full-face exposures (eyes open and closed). Clinical grading of wrinkles according to adapted version of the Glogau scale (Glogau photodamage classification scale) and clinical assessment of skin smoothness using tactile roughness grading scales were carried out at baseline and on days 1, 7, 14 and 15, and weeks 3, 4, 8 and 12.

Figure 1. Showing Light proof adhesive metal template with areas of skin for application of 20%, 10% ALA or vehicle 0.

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**Table I. Summary of phototoxic reactions with differing concentrations and occlusion times of 5-aminolaevulinic acid.**

<table>
<thead>
<tr>
<th>Occlusion time (mins)</th>
<th>Percentage ALA</th>
<th>Assessment</th>
<th>30 minutes</th>
<th>60 minutes&lt;sup&gt;a&lt;/sup&gt;</th>
<th>90 minutes&lt;sup&gt;b&lt;/sup&gt;</th>
<th>120 minutes&lt;sup&gt;c&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>5%</td>
<td>10%</td>
<td>20%</td>
<td>5%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>Day 1</td>
<td>Erythema</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Day 2</td>
<td>Pigmentation</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Day 3</td>
<td>Erythema</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Day 4</td>
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<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Day 5</td>
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<td>Day 6</td>
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</tr>
<tr>
<td>Day 7</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Day 8</td>
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<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mild textural changes to the skin; <sup>b</sup> Mild to moderate textural changes to the skin; <sup>c</sup> Severe textural changes to the skin.
Results

Forearm skin study

Minimum erythema, without significant pigmentation, was achieved with a 5% concentration of 5-ALA and an occlusion time of 30 minutes.

A 10% concentration of 5-ALA, with an occlusion time of 30 minutes, gave more consistent erythema and mild pigmentation. At 60 minutes’ occlusion, a concentration of 10% induced pigmentation in several sites with adverse textural changes to the skin.

At all occlusion times 20% concentrations of 5-ALA gave severe erythema, some ulceration and pigmentation and adverse textural skin changes (Table I).

Periorbital skin study

Five percent 5-ALA with an occlusion time of 30 minutes gave mild erythema at day 1 which was self-limiting and showed mild skin peeling at 3–7 days, which had resolved on the seventh day. Clinical assessment of the periorbital region showed a significant treatment response in four out of six subjects (67%) with a reduction in fine lines.

Discussion

A 20% concentration of 5-ALA gave too severe erythema, some ulceration and moderate textural changes of scaling, pigmentation and roughness to be practical. Longer occlusion times of 60, 90 and...
120 minutes are less practical in managing the patient. The phototoxic reaction at these occlusion times and higher concentrations gave too variable and too strong phototoxic reactions to be safe for facial treatments. The persistence of pigmentation and textural roughness of the skin would also be of major concern if this occurs on facial skin.

At 5% concentrations and 30 minutes occlusion, the results appear safe and indicative of a controlled phototoxic response.

In some patients areas such as the forehead or chest have been treated with 10% concentration and 30 minutes occlusion (Figure 6). This has resulted in good or excellent responses with minimal morbidity.

This paper has shown the reproducibility of low concentration 5-ALA to produce phototoxic response of the skin. Work using higher concentrations has been shown to be less predictable and hence complicate post treatment care. Further work is required to elucidate the benefits of repeating low concentration 5-ALA-PDT, possibly at intervals of 7–14 days to enhance the results of a single treatment.

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References
