Dose-Response and Time-Course Characteristics of UV-A1 Erythema

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Objective: To determine the time course and dose-response characteristics of UV-A1 erythema in the Tayside region of Scotland.

Design: Adult volunteers (skin types I and II [n=13] and III and IV [n=11]) were exposed to geometric dose series of UV-A1 irradiation from a high-output source on photoprotected lower back and inner forearm skin.

Setting: Photobiology unit in a university hospital.

Main Outcome Measures: The minimal erythema dose (MED) was recorded visually and erythema was assessed objectively by erythema meter at 4, 8, 24, and 48 hours after exposure.

Results: Peak erythema (lowest visual MED) was seen at 8 hours on the back and arm in 11 subjects with skin types I and II and on the back at 8 hours in 9 subjects and on the arm at 4 hours in 10 subjects with skin types III and IV. The lowest median (range) MED was 20 J/cm² (14-56 J/cm²) on the back and 42 J/cm² (20 to >80 J/cm²) on the arm at 8 hours for subjects with skin types I and II and 28 J/cm² (20-112 J/cm²) at 8 hours on the back and 56 J/cm² (28-80 J/cm²) at 4 hours on the arm for subjects with skin types III and IV. The D₀.025, an objective measure that corresponds approximately to the visual MED, demonstrated a broad peak from 8 to 24 hours.

Conclusions: Our local population is more erythmally sensitive to UV-A1 radiation than reports suggest. Daily dose regimens may risk cumulative erythema. Lower starting doses should be used in this population. The wide range of MEDs highlights the need for MED testing.

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UV-A (320-400 nm) radiation has been used for many years in combination with psoralen for the treatment of psoriasis and a range of other skin diseases. More recently, UV-A1 (340-400 nm) sources have been developed commercially. These filter out the most erythemogenic part of the UV-A spectrum (UV-A2, 320-340 nm), which, in addition to UV-B, is considered responsible for most human skin cancers, with longer wavelengths considered to be relatively safer. The development of UV-A1 phototherapy enables higher doses of longer wavelength UV-A to be delivered to a patient, thus limiting the potential for erythema and possibly carcinogenesis, while maximizing the therapeutic effect.

UV-A1 has been used for the treatment of atopic dermatitis for more than 10 years and is considered to act in part, by immunomodulation. In addition, UV-A1 has been shown to induce collagenase and reduce cross-linked collagen, leading to successful use in the scleroderma. The limiting factor for high-dose delivery has been the low output of the commercially available cabinets, requiring long exposure times to deliver the required dose, resulting in large amounts of heat generated and thus in poorly tolerated therapy. More recently, higher output sources have been developed, allowing for higher dose delivery within a practical exposure time. On this basis, “high-dose” UV-A1 therapy has been used for the effective treatment of atopic dermatitis, scleroderma, and several other skin diseases. The effect appears to be local, and therefore treatment of isolated plaques of scleroderma would limit the potential adverse effects of treatment, while targeting the therapeutic action.

See also pages 1527, 1537, 1542, 1556, 1580, and 1589

Groups investigating the use of high-dose UV-A1, have used a dose of 130 J/cm² (in comparison with conventional low-dose UV-A at approximately 20 J/cm²). This high dose was selected for use in atopic dermatitis because previous work had shown that modulation of epidermal Langerhans cells occurred at this level of exposure. Erythema is the most common adverse effect reported after narrowband UV-B or psoralen–UV-A therapy but has not been described in relation to UV-A1
therapy, even at doses in the order of 130 J/cm². In the European and North American literature, this therapy has been used with a daily fixed-dose regimen without mention of minimal erythema dose (MED) testing. However, concern has been raised about the risk of burning in fair-skinned individuals. The population in the United Kingdom has a large proportion of individuals with skin types I and II, who are more susceptible to developing erythema and long-term adverse effects from UV radiation. Before introduction, we believed it to be important to determine the safe starting doses to be used in this population to optimize therapeutic effect and minimize acute and chronic adverse effects. By assessment of a detailed time course of UV-A1 erythema, we anticipated a more accurate determination of the most suitable interval between treatments to limit avoidable adverse effects.

METHODS

Twenty-four adult volunteers (13 with skin types I and II [3 with skin type I], median age, 27 years [age range, 20-47 years], and 11 with skin types III and IV [1 with skin type IV], median age, 32 years [age range, 20-64 years]) were recruited. We excluded those with a history of photosensitivity, skin malignancy, or immunosuppression and those using potentially phototoxic or immunosuppressive medication. We also excluded pregnant or breast-feeding women and anyone who had received phototherapy or photochemotherapy in the previous 3 months. The study was approved by the Tayside committee for medical research ethics, and written informed consent was obtained from all subjects.

IRRADIATION

UV-A1 irradiation was delivered by a high-output 2-kW filtered metal halide source (Dermalight Ultra 1; Dr Hönle AG, Gräfelfing, Germany) with an emission spectrum, extending into the visible range of 340 to 440 nm (Figure 1). The device had a "cold light" reflector and filters to remove infrared light. Irradiance measured at the skin surface at a distance of 30 cm from the lamp was 70 to 77 mW/cm² using a Waldmann UV meter.

All volunteers were exposed to a geometric dose series of UV-A1 irradiation (7, 10, 14, 20, 28, 40, 56, and 80 J/cm² for those with skin types I and II, with an additional dose of 112 J/cm², while omitting the lowest dose for those of skin types III and IV; 1.4 incremental factor) at 2 test sites (photoprotected lower back and inner forearm skin; 8x1.5 cm² test areas).

ASSESSMENT

The MED (the dose of UV-A1 causing just perceptible erythema), the intensity of erythema on a scale of 1 to 4 (where 1 indicates just perceptible erythema; 2, well defined erythema; 3, erythema and edema; and 4, erythema, edema, and blisters) and the presence or absence of pigmentation were recorded visually at 4, 8, 24, and 48 hours (and additionally in 1 volunteer at 12, 15, and 36 hours) after exposure. Erythema was also assessed objectively using an erythema meter (Dia-Stron Limited, Andover, England) by taking triplicate measurements to calculate a mean increase in erythema index at each test site compared with an adjacent nonirradiated control site. Erythema meter readings were discontinued once the development of pigmentation was visible. This method is established and has been used in other studies in our department.

STATISTICAL ANALYSIS

The increase in mean erythema index at each test site compared with the nonirradiated control site was plotted against the logarithm of the UV-A1 dose and a sigmoidal dose-response curve constructed by performing iterative linear regressions to calculate best fit. The maximum slope of each dose-response curve and the dose required to produce an increase in erythema index of 0.025 (D₀.₀₂₅), which corresponds approximately to the threshold erythema detected visually, were determined. The median and range of the MED, D₀.₀₂₅ and maximum slope of the erythemal dose-response curve, which is an indicator of an individual's risk of burning during phototherapy, were compared between time points and body site using the Wilcoxon matched-pairs signed-rank test. Comparison between skin type groups was carried out using the Mann-Whitney test. No corrections were made for multiple comparisons. P<.05 was considered statistically significant, and the 95% confidence intervals (CIs) are presented. Correlation of data was analyzed using the Spearman rank correlation coefficient (r).

RESULTS

VISUAL ERYTHEMA

The erythema results for the back skin of 1 subject with skin type II who had *Pityrosporum* folliculitis were omitted from analysis because readings were uninterpretable; therefore, for subjects with skin types I and II, there were 12 results for the back skin and 13 results for the arm skin (Table). For skin types I and II, peak erythema (lowest visual MED) on the back was reached at 4 hours (median MED [range], 28 J/cm² [20-56 J/cm²]) in 7 subjects (58%). It remained maximal in 6 subjects and peaked in the remaining 5 (92% in total) at the 8-hour time point (median MED, 20 J/cm² [14-56 J/cm²]). On the arm, peak erythema was seen at 4 hours (median MED, 56 J/cm² [18-56 J/cm²]) in 10 (77%) and at 8 hours (median MED, 42 J/cm² [28 to >80 J/cm²]) in 11 subjects (85%). For those with skin types III and IV (n=11; Table), peak erythema on the back was seen at 4 hours (median MED, 40 J/cm² [14-112 J/cm²]) in 6 (55%) and at 8 hours (median MED, 28 J/cm² [20-112 J/cm²]) in 9 (82%).
the inner arm, peak erythema was seen at 4 hours (median MED, 56 J/cm² [28-80 J/cm²]) in 10 subjects (91%) and at 8 hours (median MED, 56 J/cm² [28-80 J/cm²]) in 9 (82%). Peak erythema was seen on both the back and inner arm at 12 hours in the 1 subject in whom this time point was recorded. Median time to maximal erythema was 4 hours (range, 4-8 hours) on the back and arm for all skin types. Most subjects (n=22; 96%) were at maximal erythema at 8 hours on the back, which was more sensitive to UV-A1–induced erythema compared at maximal erythema at 8 hours on the inner arm skin (Figure 2C and D) occurred at the 4-hour (P=.54) and 8-hour (P=.80) time points and occurred at 8 hours on the arm in 3 subjects. This developed in 2 subjects from 4 to 24 hours, in 1 subject from 4 to 8 hours, and in 1 subject only at 8 hours. In 1 subject this was also evident at the 56-J/cm² site on the back at 8 and 24 hours.

**OBJECTIVE ERYTHEMA**

In contrast to the visual MED in subjects with skin types I and II, which showed maximal erythema at the 4- or 8-hour time points, the D₀.025 from the dose-response curves (Figure 2A and B) showed a broad erythematic peak at the 8- and 24-hour time points, which were similar on the back and arm, with the 8-hour time point not differing significantly from the 4-hour time point on either the back or the inner arm. In subjects with skin types III and IV, the lowest D₀.025 on back and inner arm skin (Figure 2C and D) occurred at the 8-hour time point, corresponding to visual readings but again did not differ significantly from the 4-hour readings on the back or arm or from the 4-hour readings on the back.

In subjects with skin types I and II, the maximum slope of the dose-response curve occurred at 24 hours on the back (median, 0.253 [range, 0.038-0.525]) but did not differ significantly from the 8-hour (P=.36) and 48-hour (P=.54) time points and occurred at 8 hours on the arm (median, 0.124 [range, 0.034-0.510]), but again this was not significantly different from that at 4 hours (P=.73) or 24 hours (P=.20). In subjects with skin types III and IV, the maximal slope occurred at 4 hours on the back (median, 0.192 [range, 0.039-0.403]) and 24 hours (median, 0.150 [range, 0.053-0.425]) on the arm but was not significantly different from the 8-hour time point at either body site.

In subjects with skin types I and II, we were unable to plot a dose-response curve for the back at 24 hours in 3 subjects owing to insufficient erythema and at 48 hours in 4 subjects owing to pigmentation, and for the arm, at 24 and 48 hours in 1 subject owing to pigmentation and at 24 hours in 1 subject and at 48 hours in 2 subjects owing to insufficient erythema. In subjects with skin types III and IV, we were unable to plot a dose-response curve at 24 hours in 3 subjects for the back and arm skin and at 48 hours in 6 subjects for the back skin and 9 subjects for the arm skin owing to pigmentation.

**INTERINDIVIDUAL VARIATION**

The dose response and time course of visual and objective (Figure 3) erythema varied markedly between patients of all skin types and overlapped greatly between skin types at most time points. The median D₀.025 value showed a trend to increase with skin type, and the difference in median D₀.025 on the back between the skin types I and II group and the skin types III and IV group was significant at the 8-hour (P=.005) and 24-hour (P=.02) time points but failed to reach significance at the 4-hour (P=.08) and 48-hour (P=.11) time points (Figure 4A). The visual MED (Figure 4B) also showed a trend to increase with skin type, but only the difference between skin types II and III, which was significant at 8 hours (P=.003) and 24 hours (P=.008) was reliable owing to the small numbers with skin types I and IV. The lack of difference between skin types I and II was contributed to by 1 subject with skin type I who had an MED of 56 J/cm², which was higher than all but 1 subject in the skin type II group who mostly had an MED of 20 or 40 J/cm².

**BODY SITE VARIATION**

Both the median visual MED and D₀.025 values were higher for the inner arm than for the back skin. In 12 subjects with skin types I and II, the visual MED was lower on the back than on the arm (with the greatest dif-

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**Table. Peak Erythema Assessed by MED and Lowest Median MED on the Back and Inner Arm Skin**

<table>
<thead>
<tr>
<th>Skin Type</th>
<th>Peak Erythema, h</th>
<th>Lowest Visual Median MED (range), J/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>I and II</td>
<td>7 8 12 24</td>
<td>20 (14-56) at 8 h 42 (20-80) at 8 h</td>
</tr>
<tr>
<td>Back (n=12)</td>
<td>6 9 1 0</td>
<td>28 (20-112) at 8 h 56 (28-80) at 4 h</td>
</tr>
<tr>
<td>Arm (n=13)</td>
<td>10 11 0 0</td>
<td></td>
</tr>
<tr>
<td>III and IV</td>
<td>Back (n=11)</td>
<td></td>
</tr>
<tr>
<td>4 9 1 0</td>
<td>10 9 1 0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: MED, minimal erythema dose.
ference being an MED of 20 J/cm² on the back compared
with no erythema at 80 J/cm² on the arm) in 9 subjects
and was the same on the back and arm in 3 subjects at
8 hours. The visual MED was lower on the back than on
the arm in 10 subjects and was the same on the back
and arm in 2 subjects at 24 hours. At the 8-hour time
point for subjects with skin types I and II, the reading
from the inner arm did not significantly correlate with
the reading from the back ($r_s=0.432; P=.16$), but at the
24-hour ($r_s=0.713; P=.01$) time point, good correlation
was seen (Figure 5).

In 11 subjects with skin types III and IV, the visual
MED was lower on the back than on the arm in 8 sub-
jects (with the greatest difference being an MED of 28
J/cm² on the back compared with no erythema at the
112-J/cm² test site on the arm) and higher on the back
than on the arm in 3 subjects at 8 hours. The visual
MED was lower on the back than on the arm in 5 sub-
jects, the same on the back and arm in 2 subjects, and
higher on the back than on the arm in 4 subjects at 24
hours. For subjects with skin types III and IV, the read-
ing from the inner arm did not significantly correlate
with the reading from the back at either the 8-hour
($r_s=0.026; P=.95$) or the 24-hour ($r_s=0.024; P=.95$)
time points. Therefore, an MED obtained using arm skin
for testing is not a good predictor of tendency to burn
elsewhere on the body, particularly for the individuals
with skin types I and II. It also appears that for indivi-

Figure 2. $D_{0.025}$ values at each time point for subjects with skin types I and II on the back (A) and arm (B) and for subjects with skin types III and IV on the back (C) and arm (D). Data points represent $D_{0.025}$ values for 1 individual. Data are given as median values.

Figure 3. $D_{0.025}$ values at each time point for subjects with skin types (STs) I and II and III and IV on the back.
als with skin types III and IV, the MED on the arm may be lower than on the back and therefore it may be advisable to perform MED testing at both sites in this skin type population.

ADVERSE EFFECTS

One subject with skin type III who had an MED of 28 J/cm² on the back at all time points and 80 J/cm² on the arm at the 8-hour time point experienced normal fading of erythema within days of irradiation but developed an eczematous reaction within some of the test sites on the back 8 weeks later (Figure 6A). Another subject with skin type II reported itchy, erythematous reactions at some test sites on the back and arm (MEDs of 20 and 40 J/cm², respectively, at 8 hours) 5 weeks later, and a similar response was seen 6 weeks after irradiation on the back of an individual with skin type I (Figure 6B) who had participated in the original pilot of this study and had an MED of 15 J/cm² on the back and arm at 24 hours. None had a history of photosensitivity or had positive findings on lupus serologic testing.

While the literature suggests that high UV-A1 doses can be used without burning, our patient population seems to be at far greater risk than would be expected. The early visual erythemal peak (4-8 hours) may suggest that daily dose regimens would be possible without the risk of cumulative erythema, but the objective erythema meter readings suggest that the time course of erythema is broad, with the peak extending to the 24-hour time point, particularly in individuals with skin types I and II, suggesting that cumulative erythema may be a significant risk with the use of a daily dose regimen. The visual erythema peak at 8 hours reached in 96% of subjects also suggests that reading the MED at 24 hours, as is often carried out for practical reasons, will miss peak ery-
Erythema was seen in all skin types in our population at much lower doses than those used in most published dose regimens. There was a wide range of $D_{0.025}$ and visual MED values within each skin type and significant overlap between skin types, which has been shown for psoralen–UV-A and UV-B erythema, highlighting the need for MED testing before therapy. In contrast to published dose regimens of 130 J/cm², we suggest that doses as low as 14 J/cm² should be included in geometric dose series for all skin types. This would help to avoid adverse effects of burning, while allowing for higher starting doses in those who do tolerate them, which may in turn lead to fewer treatments and lower total doses being used in those individuals. However, median $D_{0.025}$ and visual MED values tended to increase with skin type, although only the difference between skin types II and III, which was significant, was reliable owing to the small numbers with skin types I and IV. The development of erythema and edema in response to doses of 56 and 80 J/cm² in individuals with skin types I and II also highlights the need for MED testing before whole body therapy. It is also of interest that 2 subjects with skin type II had developed pigmentation on the back and arm at 48 hours after irradiation, while in those with skin type III, pigmentation did not develop on the back and arm in 5 and 2 subjects, respectively. The development of an eczematous response at the higher test dose sites 6 to 8 weeks after MED testing was unexpected and remains unexplained in the absence of a history of photosensitivity.

The slopes of the dose-response curves in response to UV-A1 irradiation appear similar to those reported in response to oral psoralen–UV-A and narrowband UV-B and less steep compared with broadband UV-B, although comparisons between studies should be interpreted with caution. The shallow dose-response curve for UV-A1 erythema may result in limitation in subjective visual assessment, which relies on a threshold of visual detection and suggests that, when possible, objective measurement should also be carried out with construction of accurate dose-response curves. The greater sensitivity of the back and the poor correlation between the MED obtained from testing on back and arm skin suggests that the back should be the chosen site for MED testing, although additional body sites and time points should be investigated. In the individual in whom 12-hour and 15-hour time points were investigated, peak visual and objective erythema occurred at the 12-hour and 15-hour time points, respectively, so that late afternoon testing followed by early morning reading may allow a more accurate assessment of MED.

Why the individuals in this population develop erythema at much lower doses than those reportedly used...
in the literature is unclear. Differences in spectral emission of the source used and dosimetry are possible, but the emission spectrum of the source used in this study revealed that lamp emission of wavelengths less than 340 nm was negligible and therefore cannot account for the increased tendency to develop erythema. Differences in dosimetry, however, may be relevant.

This study provides important data on the dose response and time course of UV-A1 erythema, which to our knowledge has not been previously reported. These findings are clinically relevant because phototherapy using this waveband has recently been introduced into the United Kingdom and may increasingly be used to treat a wide range of skin diseases, which has been facilitated by the development of high-output sources allowing delivery of high-dose therapy. The wide variation in dose response and time course characteristics of erythema between and within skin types and between body sites highlights the need for further investigation at different body sites and time points to determine the optimum site for MED testing and time for MED assessment.

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REFERENCES