The Time Course of Topical PUVA Erythema Following 15- and 5-Minute Methoxsalen Immersion

Irene Man, MRCP; Yew Kai Kwok, MRCP; Robert S. Dawe, MD; James Ferguson, MD; Sally H. Ibbotson, MD

**Background:** Limited data exist in the literature concerning the characteristics of erythema following psoralen UV-A (PUVA) treatment using topical methoxsalen. To optimize the phototherapeutic regimen and reduce short- and long-term risks, knowledge of such basic information is essential.

**Observations:** The characteristics of PUVA erythema following 15- and 5-minute immersion in methoxsalen was determined. The PUVA erythema after 15-minute methoxsalen immersion exhibited a broad peak, with the lowest median minimal phototoxic dose (MPD) at 96, 120, and 144 hours after UV-A irradiation. Seventy-three percent of subjects experienced peak erythema at 120 hours compared with only 45% at 72 hours. From the dose-response data, an increase in the erythema index of 0.025 (equivalent to the MPD) was significantly lower when determined at 120 hours after UV-A irradiation than at 72 hours (P=.03). The median maximum slope of the dose-response curve occurred at 144 hours. After 5-minute immersion, PUVA erythema displayed a broad peak from 72 hours. Erythema summation scores followed a trend similar to that of 15-minute immersion, but the intensity was significantly reduced.

**Conclusions:** Methoxsalen–UV-A erythema exhibited a broad plateau between 96 and 144 hours, with most subjects at peak erythema at 120 hours. Reduction of methoxsalen immersion time significantly lowered the erythematous intensity. Minimum phototoxic dose reading at 72 hours underestimates the phototoxic effect of topical methoxsalen PUVA, and a change in the MPD assessment time should be considered.

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**BATH PSORALEN UV-A irradiation (PUVA) therapy is an effective alternative to oral PUVA treatments.** Despite the widespread use of bath PUVA, limited experimental studies exist on the nature of PUVA phototoxic effect with a view to optimization of therapy.

As is the case with oral PUVA, erythema in nonlesional skin is the main limiting factor that determines the dose of UV-A radiation administered during treatment. Prior to each treatment course, determination of the minimal phototoxic dose (MPD) at 72 hours after UV-A irradiation is recommended to ensure a safe starting dose. This is based on the conventional view that peak PUVA erythema occurs between 48 and 72 hours after UV-A irradiation. Although this is often quoted in the literature, there are no experimental data to support this statement.

Contrary to these assumptions, Ibbotson and Farr recently showed that peak PUVA erythema following oral administration of methoxsalen did not occur until 96 hours or later in 75% of subjects. Initial work with methoxsalen diluted in bath water and with cream and gel formulations also demonstrated a delayed erythemal peak beyond 72 hours. Objective assessments and dose-response characteristics were not examined in these latter studies. We therefore conducted the present study to investigate in detail the time course and dose-response characteristics of PUVA erythema in skin photosensitized by bath methoxsalen.

Currently, the British Photodermatology Group recommends a 15-minute psoralen bathing time prior to immediate UV-A irradiation. However, the optimal immersion time and clinical efficacy remain to be investigated in a controlled clinical study. Recently, it has been suggested that a reduction to a 5-minute soak may be as therapeutically effective as the standard 15-minute immersion time, and in a retrospective study that compared 10- and 5-minute methoxsalen soak times prior to UV-A exposure in the treatment of psoriasis, similar efficacies were demonstrated.
There is no box at 48 hours because most of the results fell at the median value.

Intraindividual comparisons using methoxsalen bath to 5 minutes influenced the PUVA erythema peak response between 96 and 144 hours. For 5-minute immersion, they were at peak response at 120 hours; for 5-minute immersion, they were at peak response at 120 hours; for 15-minute immersion, most subjects (ie, lowest minimal phototoxic dose) at each evaluation time for 15- and 168-hour evaluation times after 15-minute methoxsalen immersion (n=22). The median lowest MPD occurred at 96, 120, and 144 hours. This was not significant compared with 72 hours. The dark horizontal lines indicate median values; boxes, interquartile ranges; error bars, values adjacent to the interquartile ranges; and circles, outliers. There is no upper error bar at 96 hours because most of the results at 96 hours fell within the interquartile range. Likewise, there is no box at 48 hours because most of the results fell at the median value.

To determine whether a reduction in the duration of the psoralen bath to 5 minutes influenced the PUVA erythemal time course, we made intraindividual comparisons using 15- and 5-minute immersion times.

### METHODS

#### SUBJECTS

Ethical approval was obtained from the Tayside Research Ethics Committee, Dundee, Scotland. Twenty-two healthy adult volunteers (14 women) with skin types I (n=2), II (n=17), and III (n=3) were recruited following informed consent. The median age was 34 years (age range, 18-55 years). None of the subjects were receiving phototoxic medication. Exclusion criteria were pregnancy, breastfeeding, history of photosensitivity, and UV exposure in the 3 months prior to recruitment.

#### METHODS

One forearm was immersed in 1.2% methoxsalen solution (Crawfords Pharmaceuticals, Milton Keynes, England; concentration, 3.0 mg/L) for 15 minutes. In 13 of the 22 subjects, the contralateral forearm was immersed for 5 minutes. The skin was gently dried and eight 1.5-cm² test sites on the flexor forearm(s) were immediately exposed to a UV-A dose series (0.1, 0.15, 0.22, 0.33, 0.56, 0.82, 1.2, and 1.8 J/cm²; 1.5-1.7 incremental factor). The UV-A source was delivered using a broad-spectrum UV-A fluorescent lamp (ten 0.6-m Waldmann F15W/T8 tubes [Villingen-Schwenningen, Germany]); peak wavelength, 350 nm; wavelength range, 320-400 nm). The irradiance was 5.7 mW/cm² at a distance of 20 cm, measured using a Waldmann UV meter. Test sites on each subject’s unsensitized upper back or flexor forearm were exposed to identical UV-A dose ranges to ensure that erythema did not occur with UV-A irradiation alone.

Erythema at each irradiated test site was assessed visually and objectively at 24-hour intervals for 7 days after UV-A irradiation. At each evaluation time, the UV-A dose required to induce just perceptible erythema in psoralen-sensitized skin (minimal phototoxic dose [MPD]) was determined. In addition, to separate the erythema response, erythema summation scores were calculated: that is, the grades of erythema at the irradiated sites were summed. A score of 1 indicated just perceptible erythema; 2, definite well-defined erythema; 3, erythema with edema; and 4, erythema with blistering.

Objectively, erythema was quantified using a reflectance instrument. Measurements from each irradiated site and adjacent nonirradiated skin were taken in triplicate. The difference between the mean erythema index of unirradiated skin and irradiated skin was calculated and plotted against the logarithm of the UV-A radiation dose. A sigmoidal dose-response curve was fitted to the data using a logit function and computer fit. For each curve, the dose of UV-A radiation required to cause an increase in the erythema index of 0.025 (D₀.₀₂₅) (clinically equivalent to the MPD) and the maximum slope were determined. The slope of the erythemal dose-response curve provides an indication of an individual’s risk of developing phototoxic erythema.

### STATISTICAL ANALYSIS

Values were expressed as median (range). The lowest MPD or D₀.₀₂₅ (indicating peak erythema) and the maximum slope of the dose-response curve were compared with the data at the conventional time point of 72 hours. Significance of the data (taken as P<.05) was determined using the Wilcoxon matched-pairs signed-rank test. No corrections were made for multiple comparisons.

### RESULTS

#### 15-MINUTE METHOXSALEN IMMERSION

Visually, erythema was evident in 95% of subjects at the first assessment time 24 hours after UV-A irradiation. At each subsequent assessment time, the MPD gradually decreased, reaching a broad peak with a trend toward the lowest median value at 96, 120, and 144 hours (0.33 J/cm²; range, 0.11-0.82 J/cm²) (Figure 1). This was not significant when compared with the 72-hour value (0.45 J/cm²; range, 0.15-0.82 J/cm²; P=0.47, P=.10, and P=.38 for comparison with the MPDs determined at 96, 120, and 144 hours, respectively). Sixteen subjects (73%) reached peak erythema at 120 hours (Figure 2), while only 10 (45%) were at peak response at the conventional reading time of 72 hours and at 96 hours. The median time to reach the lowest MPD was 96 hours (range, 48-144 hours).

Results of objective assessment were available in 18 subjects. Four others did not develop sufficient ery-
In sixteen subjects (89%), the lowest D0.025 occurred at or the lowest value at 72 hours (0.56 J/cm²; range, 0.22-1.8 J/cm²). This value remained low up to 168 hours. A reduction in the methoxsalen immersion time from 15 minutes to 5 minutes resulted in a significant increase in the erythema index of 0.025 (n=18) for 15-minute methoxsalen immersion. The dark horizontal lines indicate median values; boxes, interquartile ranges; error bars, values adjacent to the interquartile ranges; and the asterisk at 120 hours, the D0.025 was significantly lower at 120 than at 72 hours (P=.03). The dose-response data revealed a pattern that corresponded to the visual MPD data. A broad plateau was apparent from 96 hours onward, and the median D0.025 was significantly lower at 120 hours than at 72 hours (P=.003) (Figure 3). In sixteen subjects (89%), the lowest D0.025 occurred at or beyond 96 hours. The median maximum slope of the dose-response curves occurred at 144 hours (317; range, 84-483), and this was significant when compared with the slope at 72 hours (165; range, 43-441; P=.01).

5-MINUTE METHOXSALEN IMMERSION

Erythema was detectable in 11 (85%) of 13 subjects at 24 hours, and a broad erythemal peak was demonstrated. The median MPD gradually declined and reached the lowest value at 72 hours (0.56 J/cm²; range, 0.22-1.8 J/cm²). This value remained low up to 168 hours (Figure 4). Six subjects (46%) were at peak erythema between 96 and 144 hours (Figure 2). Construction of dose-response curves was not possible because of insufficient erythema induced at the test sites. Four subjects developed faint pigmentation at and beyond 144 hours.

INTRA-INDIVIDUAL COMPARISON OF 15- AND 5-MINUTE IMMERSIONS

A reduction in the methoxsalen immersion time from 15 minutes to 5 minutes resulted in a significant increase in the MPD at all assessment times (P<0.05) except for 168 hours. At the clinically relevant evaluation time of 72 hours, the median MPD following 15-minute methoxsalen immersion was 0.445 J/cm² compared with 0.56 J/cm² after 5-minute methoxsalen immersion (P=.01).

The intensity of erythematic responses was compared using erythema summation scores. As shown in Figure 5, both immersion times followed a similar trend with a peak score at 120 hours. This was statistically significant when compared with the summation scores at 72 hours (P=.003 at 15 minutes; P=.01 at 5 minutes). The erythemal intensity at all evaluation times was significantly lower for 5-minute immersion than 15-minute immersion (P<.01).

COMMENT

Erythema is an important end point in PUVA therapy. Since the introduction of PUVA, treatment-induced erythema has been assumed to occur 48 to 72 hours after UV-A irradiation. This assumption formed the basis for MPD determination at 72 hours and for the generally accepted practice of administering PUVA treatments at least 72 hours apart. Furthermore, MPD readings at 72 hours have been widely used for assessment of peak erythema in clinical and experimental PUVA studies. At variance with this assumption, recent evidence suggests that maximum PUVA erythema occurs beyond 72 hours. In 16 volunteers photosensitized by oral methoxsalen, Ibbotson and Farr demonstrated that maximum PUVA erythema occurred at or beyond 96 hours in 75% of subjects. Similarly, work conducted with topi-
cal methoxsalen in 10 subjects showed that maximum visible erythema occurred up to 120 hours after UV-A exposure.\textsuperscript{10} Preliminary data with cream and gel formulations of methoxsalen have also shown a similar delayed erythema peak.\textsuperscript{11}

In the present study, in keeping with previous publications, maximum response occurred beyond 72 hours. Visually, a broad peak was evident in most cases between 96 and 144 hours after UV-A irradiation. Seventy-three percent of subjects reached and sustained peak erythema at 120 hours. By 72 hours after UV-A irradiation, only 43% of the subjects had reached maximum response. Objectively, most subjects had maximum erythema at or beyond 96 hours, and the median lowest value was significantly lower at 120 hours than at 72 hours.

It is known that the duration of psoralen immersion time influences the PUVA erythematous sensitivity. In a preliminary study by Azurdia et al,\textsuperscript{12} the slope of the dose-response curve after 15-minute methoxsalen immersion was significantly steeper than that for a 5-minute immersion. Dolezal et al\textsuperscript{13} also demonstrated that by increasing the methoxsalen immersion time from 5 minutes to 30 minutes, a greater than 60% reduction in the determined MPD occurred. Similarly we demonstrated that a reduction of methoxsalen immersion time from 15 minutes to 5 minutes significantly increased the median MPD by 70% as determined at 96, 120, and 144 hours.

The effect on clinical efficacy after 5-minute immersion is not known. Initial data from a retrospective study suggested similar efficacies after 10 and 5 minutes of methoxsalen immersion in the management of psoriasis.\textsuperscript{12} Further controlled studies are needed to examine this. If 5 minutes of methoxsalen immersion followed by UV-A exposure proves to be as effective as the current standard regimen, it will have a considerable impact in clinical practice by saving time for patients and nursing staff.

In summary, we have shown that PUVA erythema after standard methoxsalen immersion exhibits a broad plateau of peak response from 96 to 144 hours after UV-A irradiation, with the objective erythemal readings demonstrating a significant peak at 120 hours rather than the previously assumed 72 hours. Reduction of the immersion time to 5 minutes also showed a broad plateau effect from 72 hours, and the erythemal intensity was significantly reduced.

Our data confirm that the currently accepted MPD assessment time of 72 hours underestimates the phototoxic effect of topical PUVA. This coupled with twice-weekly treatments before standard erythema is reached could potentially result in cumulative erythema and an increased risk of burning during PUVA. A change in the practice of MPD determination time should be considered. In addition, increasing the interval between PUVA treatments may further reduce erythema risk. However, further studies are needed to examine the effect of these changes in treatment outcome and phototoxic effect.

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Corresponding author and reprints: Irene Man, MRCP, Photobiology Unit, Department of Dermatology, Ninewells Hospital and Medical School, Dundee, DD1 9SY Scotland (e-mail: iwman@yahoo.com).

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