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INVESTIGATIVE REPORT

# Kinetics of Phototoxicity in Trioxysalen Bath Psoralen plus Ultraviolet A Photochemotherapy

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**A trioxysalen bath is a safe alternative to systemic 8-methoxypsoralen in long-term psoralen plus ultraviolet A (PUVA) treatment. The kinetics of its main side-effect, the strong phototoxicity, has not been thoroughly studied. This study determined the degree and persistence of phototoxicity after a single 10 min bath at a trioxysalen concentration of 0.33 mg/l. The buttock skin of 16 healthy volunteers was irradiated with UVA 10 min, and 1, 3, 9 and 24 h after the bath. The minimal phototoxic dose (MPD) was assessed 48, 72 and 96 h after the bath. In general, the 96 h reading showed the lowest values of MPD; for example, a median of 0.14 J/cm$^2$ (95% confidence interval 0.10–0.14 J/cm$^2$) at sites irradiated 10 min after the bath. The values increased progressively with later irradiation, and the maximum dose applied, 18.32 J/cm$^2$, failed to produce any redness when irradiation was given 24 h after the bath. Substantial phototoxicity persists up to at least 9 h after the trioxysalen bath, making it wise for patients to avoid sunshine for at least the rest of the day.** ***Key words: dose–response relationship; minimal phototoxic dose; psoralen; trimethylpsoralen; UVA.***

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In the 1970s Fischer & Alsins (1) introduced trioxysalen [TMP; 4,5′,8-trimethylpsoralen; trioxsalen (USP); trioxysalen (rINN); CAS No. 3902-71-4] bath psoralen plus ultraviolet A (PUVA) for the treatment of psoriasis. It is an elegant alternative to systemic PUVA, without systemic side-effects such as nausea, vomiting, drug interactions and effects on liver function (2–6). Phototoxic erythema of the skin is the most feared side-effect (2, 5, 7, 8).

In bath PUVA, photosensitization is achieved by bathing in psoralen-containing tap water (1). The chemical structure of psoralen, its concentration, the temperature of the bath water, the duration of bathing, and the time interval between the bath and UVA exposure influence the phototoxicity (9, 10). In Sweden and Finland, trioxysalen bath PUVA is widely used with a standard dilution of 50 mg trioxysalen in 150 litres of tap water (1, 2, 4), or even more diluted in special cases (11). Elsewhere in Europe, 8-methoxypsoralen (8-MOP) bath PUVA is preferred (12, 13). The first systematic studies on UVA photosensitization after trioxysalen bath were performed by Fischer & Alsins in the 1970s using dysprosium lamps (1). Later, Koulu & Jansén (14) studied the phototoxicity of trioxysalen using a dilute concentration of 0.2 mg/l. In 1984, the trioxysalen preparation was approved in Finland, and it is labelled for use at a dilution of 50 mg/150–200 l, i.e. 0.25–0.33 mg/l. Hannuksela-Svahn et al. (15, 16) have shown that the long-term safety profile of trioxysalen bath PUVA is good.

This study evaluated the phototoxic properties of trioxysalen baths using the approved trioxysalen preparation at the labelled dilution and ordinary fluorescent UVA tubes under standardized conditions.

## MATERIALS AND METHODS

The Independent Ethics Committee of the Päijät-Häme Central Hospital approved the study. All volunteers gave their informed consent to participation. The study was implemented during the winter months between November 1999 and April 2000, when natural UV exposure from the sun at this latitude (61° N) was negligible.

### *Volunteers*

Sixteen healthy volunteers (9 men and 7 women) were enrolled in the study. Their mean age was 54 years (range 37–69 years). Six volunteers (3 men and 3 women) were classified in the anamnestic skin phototype group II and 10 (6 men and 4 women) in the skin phototype group III (17). Subjects under the age of 18 years or with a history of photosensitivity were not included, nor were volunteers taking medicines with photosensitizing potential. The minimum time since exposure to ultraviolet radiation (UVR), including sunbathing and phototherapy, had to be 3 months. UVA photosensitivity was examined by initial UVA minimal erythema dose (UVA-MED) phototesting consisting of 4 UVA doses ranging from 6.48 to 18.32 J/cm$^2$. All volunteers tolerated the UVA dose of 18.32 J/cm$^2$ without reaching the UVA-MED threshold at 24 h.

### *Trioxysalen baths*

A commercial alcoholic solution of trioxysalen 50 mg/100 ml (Tripsor®; Orion Corporation, Orion Pharma, Espoo, Finland) was diluted in 150 litres of tap water to produce a standard 0.33 mg/l bath concentration. The temperature of the bath water was +37°C and the duration of bathing was 10 min. After the bath the skin was gently dried, without rubbing of the test area.

### *Phototesting equipment*

All UVA irradiation series were performed with a Waldmann 801K panel (Waldmann, Schwenningen, Germany) equipped with 6 Philips Performance Sunlamp 40 W UV-A tubes. The UVA irradiance of the device was measured using a calibrated spectroradiometer, Optronic 742 (Optronic Laboratories, Orlando, FL, USA) and a broad-band UV meter (Waldmann Type 585 200 000, No. 10093), which was calibrated against the spectroradiometer. The latter was used for the follow-up of irradiance during the study. With the spectroradiometer, the UVA irradiance at skin level (21 cm from the tubes) was 7.17 mW/cm$^2$.

### *Ultraviolet A dosing*

Five geometric series of UVA were applied to the buttock skin in 1 cm$^2$ test squares. Seven or eight UVA doses were given in each

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series, with the consecutive doses increased by a factor of $\sqrt{2}$ to produce an increasing geometric dose series (Table I). The first series of UVA was given within 10 min of the bath, and the following exposures took place 1, 3, 9 and 24 h after the bath.

*Minimal phototoxic dose*

The test areas were assessed visually at 48, 72 and 96 h after the bath and classified as producing (i) no erythema in the test square, (ii) faint erythema with no clear-cut borders, (iii) faint but detectable erythema with sharp borders (defined as minimal phototoxic dose, MPD), (iv) vivid erythema with oedema, or (v) erythema with blisters. In 3 volunteers the tests were also read at 120 and 144 h. The reading time of the MPD is indicated in the text and Tables as a subscript.

*Statistical analysis*

Time-dependent differences in phototoxic doses were tested by the Wilcoxon signed rank sum test. A two-tailed $p$-value of 0.05 was considered significant. The 95% confidence intervals (CIs) for the difference in the MPD response rates were calculated.

## RESULTS

The effect of a time delay between the bath and UVA exposure on the median and the 10th and 90th percentiles of the $MPD_{96h}$ is shown in Fig. 1. Relative to the 10 min series, the MPD was increased by a factor of 2.5 when irradiation was 1 h after the bath, by a factor of 8.2 at 3 h and by a factor of 55.9 at 9 h after the bath, and the increase in MPD was highly significantly different from one UVA exposure series to the next (10 min vs 1 h, $p < 0.001$; 1 h vs 3 h, $p < 0.001$; 3 h vs 9 h, $p < 0.001$). The same phenomenon was detected at all reading points (48, 72 and 96 h). Some of the phototoxic potential of trioxysalen was still left at 9 h after the bath (Table II), but not at 24 h using the highest test dose of 18.32 J/cm$^2$.

Table II shows the median MPD values and 95% CIs for the response rates at different MPD reading points for the UVA irradiation series performed 10 min, and 1, 3 and 9 h after the trioxysalen bath. Table III shows the corresponding individual MPD values. In all UVA irradiation series, the erythema reactions peaked 96 h after the trioxysalen bath, but the MPD erythema was not yet visible in all subjects at 48 h (Table III). The same decline in the MPD was seen in the 1, 3 and 9 h test series read at 48, 72 and 96 h from the bath (data not shown). In 3 volunteers (nos 2, 5 and 7) the MPDs were also read at 120 and 144 h, but no further decrease was observed (data not shown). The phototoxicity responses showed up to four-fold interindividual variation irrespective of skin type (Table III). In the UVA irradiation series implemented 10 min after the bath, the erythema reactions were

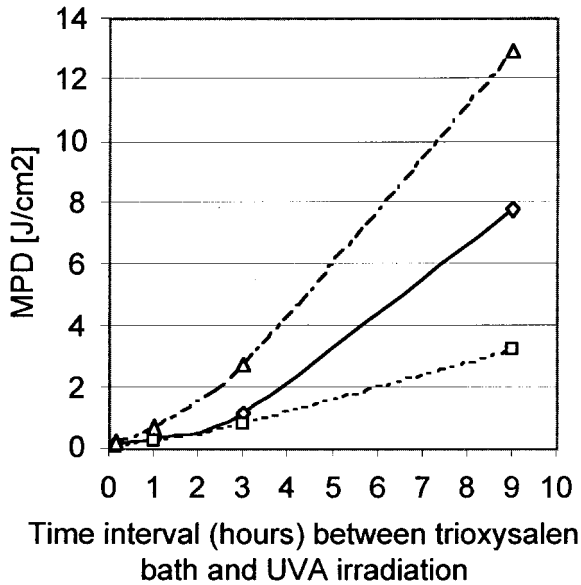


*Fig. 1.* Minimal phototoxic dose (MPD) evaluated 96 h after the trioxysalen bath in 16 volunteers. Tested skin areas were irradiated with ultraviolet A (UVA) 10 min, and 1, 3 and 9 h after the bath. ◇: Median; □ :10th percentile; △: 90th percentile.

strong or even oedematous in some sensitive individuals, but no blisters were seen. In the 1, 3, 9 and 24 h series, the erythema reactions were weak, even when sharp borders were present.

## DISCUSSION

Customarily, trioxysalen PUVA is given three times a week. This study confirmed that erythema was not maximally present until the third or fourth day after the trioxysalen bath. The same finding was made by Koulu & Jansén (14), who showed maximal erythema after trioxysalen bath and UVA to persist for up to 5 days, declining thereafter. This means that repeated suberythemal UVA doses may lead to skin burns if new exposures are given too early, creating a cumulative phototoxic effect, i.e. cumulative UVA doses exceed the $MPD_{96h}$ values. The present results suggest that the MPD of trioxysalen bath PUVA should preferably be read at 96 h. The same holds for 8-MOP bath PUVA, as noted by Calzavara-Pinton et al. (18) and Gruss et al. (10).

Consistent with an earlier finding by Fischer & Alsins, in the present study the phototoxicity vanished within 24 h of

Table I. *Increasing geometric ultraviolet A (UVA) series used in the minimal phototoxic dose testing*

| UVA irradiation time after the bath | UVA doses (J/cm$^2$) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Series | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 6 | Dose 7 | Dose 8 |
| 10 min | 0.035 | 0.05 | 0.07 | 0.10 | 0.14 | 0.20 | 0.29 | – |
| 1 h | 0.07 | 0.10 | 0.14 | 0.20 | 0.29 | 0.41 | 0.57 | 0.81 |
| 3 h | 0.29 | 0.41 | 0.57 | 0.81 | 1.15 | 1.62 | 2.19 | 3.24 |
| 9 h | 1.62 | 2.19 | 3.24 | 4.58 | 6.46 | 9.16 | 12.96 | 18.32 |
| 24 h | 1.62 | 2.19 | 3.24 | 4.58 | 6.46 | 9.16 | 12.96 | 18.32 |

Irradiations were performed at 10 min, and 1, 3, 9 and 24 h after the trioxysalen bath. Each series included seven to eight UVA doses.

Table II. *Minimal phototoxic doses (MPD; J/cm$^2$) recorded 48, 72 and 96 h after the bath with different timings of ultraviolet A (UVA) irradiation*

| Timing of reading | UVA with 10 min delay | UVA with 1 h delay | UVA with 3 h delay | UVA with 9 h delay |
|---|---|---|---|---|
| $MPD_{48h}$ ($n = 15$) | 0.20 (0.14–0.29) | 0.57 (0.57–1.15) | 1.91 (1.15–2.19) | 12.96 (12.96–12.96) |
| $MPD_{72h}$ ($n = 16$) | 0.14 (0.07–0.20) | 0.41 (0.29–0.57) | 1.62 (0.81–2.19) | 9.16 (4.58–12.96) |
| $MPD_{96h}$ ($n = 16$) | 0.14 (0.10–0.14) | 0.35 (0.29–0.41) | 1.15 (0.81–2.19) | 7.82 (3.24–12.96) |

Data are presented as median (95% confidence interval).

Table III. *Individual minimal phototoxic doses (MPD; J/cm$^2$) of 16 volunteers 48, 72 and 96 h after the trioxysalen bath; ultraviolet A irradiations were initiated 10 min after the trioxysalen bath*

| Subject/gender | Skin phototype | $MPD_{48h}$ | $MPD_{72h}$ | $MPD_{96h}$ |
|---|---|---|---|---|
| 1/F | II | 0.14 | 0.10 | 0.07 |
| 2/F | II | 0.10 | 0.07 | 0.07 |
| 3/F | II | 0.20 | 0.20 | 0.14 |
| 4/M | II | 0.20 | 0.14 | 0.20 |
| 5/M | II | 0.29 | 0.20 | 0.10 |
| 6/M | II | 0.14 | 0.07 | 0.10 |
| 7/F | III | 0.20 | 0.14 | 0.14 |
| 8/F | III | 0.10 | 0.07 | 0.05 |
| 9/F | III | 0.20 | 0.14 | 0.14 |
| 10/F | III | 0.29 | 0.20 | 0.14 |
| 11/M | III | 0.14 | 0.14 | 0.10 |
| 12/M | III | 0.20 | 0.20 | 0.14 |
| 13/M | III | 0.29 | 0.20 | 0.20 |
| 14/M | III | na | 0.29 | 0.20 |
| 15/M | III | 0.20 | 0.14 | 0.10 |
| 16/M | III | 0.29 | 0.14 | 0.14 |

F: female; M: male; na: not assessable.

the bath (1). Because UVA exposures are time-consuming to perform, the highest UVA dose studied was 18.32 J/cm$^2$. This is not high enough to test whether the cumulative natural UVA exposure from the sun during 1 day can elicit the phototoxic reaction. At the latitudes in this part of Finland the cumulative 1-day UVA dose in summer may exceed 100 J/cm$^2$. The authors recommend, therefore, that trioxysalen bath PUVA treatment should be avoided in summer at all latitudes, and that this treatment modality should not be used in clinics situated in areas with very sunny climates.

The concentration of trioxysalen baths typically varies with the study, which makes it difficult to compare results. Fischer & Alsins (1) used concentrations as high as 0.5 mg/l, recording a mean (log) $MPD_{48h}$ of 0.8 J/cm$^2$. The present investigation used a lower bath concentration of 0.33 mg/l and recorded a median $MPD_{48h}$ of 0.2 J/cm$^2$, which is only one-quarter of the dose recorded by Fischer & Alsins (1). Thus, unexpectedly, dilution of the bath led not to an increase in $MPD_{48h}$ but to a decrease. The differences in the trioxysalen preparations, UVA sources and their calibration, and the interindividual variation could probably explain this result. Of interest for further study is whether a decrease in the concentration of trioxysalen bath would facilitate the dosing of UVA. It would also be of interest to know whether the efficacy remains the same if the concentration of trioxysalen is substantially decreased. The four-fold interindividual variation in phototoxicity recorded (Table III) is consistent with the study by Koulu & Jansén (19).

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