PUVA therapy for psoriasis: Comparison of oral and bath-water delivery of 8-methoxypsoralen

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A direct clinical comparison has been made of the efficacy of oral 8-methoxypsoralen with bath-water delivery of 8-methoxypsoralen during psoralen ultraviolet A (PUVA) phototherapy for a group of forty patients with stable plaque-type psoriasis vulgaris. The 8-methoxypsoralen concentration was 3.7 mg/liter in the bath water. The efficacy of these treatments was assessed by their ability to improve or clear the psoriasis. The skin of eight of the twenty patients with oral psoralen cleared, and another eight showed good improvement. Of the twenty patients who received 8-methoxypsoralen in bath water, eight patients had clearing of the skin, whereas nine patients had good improvement during the initial 8-week treatment period. Administration of 8-methoxypsoralen in bath water required much lower ultraviolet A irradiance to achieve maximum improvement. There were no systemic side effects in the patients treated by bath-water delivery; however, some patients did develop phototoxic erythema. Minimal phototoxic doses were also studied in patients and in volunteers using both routes of psoralen delivery. The minimal phototoxic dose threshold after psoralen bath delivery gradually declined over five treatments from 5.3 ± 0.6 joules/cm^2 to 2.8 ± 0.3 joules/cm^2, suggesting an accumulation of psoralen in the skin with this method of drug delivery. Bath-water delivery of 8-methoxypsoralen was therefore found to be as effective as oral administration of 8-methoxypsoralen and yet required smaller amounts of ultraviolet A radiation and yielded fewer side effects. It would thus seem to be confirmed as a useful alternative means of 8-methoxypsoralen administration in PUVA therapy. (J AM ACAD DERMATOL **14**:754-760, 1986.)

The use of psoralens plus ultraviolet A (PUVA) is an effective therapy for the treatment of some patients with psoriasis vulgaris.[1,2] Most studies in the United States have used oral 8-methoxypsoralen; however, administration of psoralens in a dilute bath-water solution may be an effective alternative route of therapy, as suggested by previous European studies.[3]

One potential advantage of topical psoralen therapy is the absence of systemic side effects such as nausea and cataractogenesis. Another is that smaller amounts of ultraviolet A radiation are required to produce a phototoxic response, in comparison with the amounts needed to produce a response following oral 8-methoxypsoralen.[4]

Topical psoralen therapy has been proposed,[5] but one disadvantage with topical 8-methoxypso-

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ralen therapy (when the 8-methoxypsoralen is applied as an ointment, cream, or lotion) is a patchy and persistent hyperpigmentation response[6] and an uneven phototoxic response. This problem has led to the use of topical 8-methoxypsoralen lotions, ointments, or creams mainly for localized psoriasis in clothed areas or on the palms and soles.

Conversely, bath-water delivery of the psoralen would be expected to give a uniform distribution of drug over the entire immersed skin and thus would be more practical for patients with more diffuse cutaneous disease. Trioxsalen bath-water photochemotherapy was shown to be effective for psoriasis.[7]

The purpose of this study, therefore, was to closely compare the initial effectiveness of bath-water delivery of 8-methoxypsoralen with oral administration of the drug during PUVA therapy for chronic, extensive psoriasis at the same institution in a group of age- and severity-matched patients with psoriasis.

In addition, the minimal phototoxic doses for 8-methoxypsoralen delivered to the skin by psoralen bath-water immersion were examined after single and repeated exposures in lieu of previous reports of declining minimal phototoxic doses with repeated exposures.[4]

PATIENTS AND METHODS

Patients had chronic plaque psoriasis for at least 1 year prior to the start of this investigation. They had all stopped using topical therapy except for emollients for 2 weeks prior to the start of the investigation and during its first 6 weeks.

Patients who were treated with 8-methoxypsoralen in bath water plus ultraviolet A were approximately matched by age and severity with a group of patients who had been treated with oral 8-methoxypsoralen plus ultraviolet A over the previous 3 months. All patients who completed the study started and finished their therapy between October and March, and sunbathing was not allowed during the study.

Relevant patient characteristics are summarized in Table I.

Table I. Detail of patients receiving 8-methoxypsoralen by bath-water or oral delivery plus ultraviolet A phototherapy

	Bath-water delivery	Oral delivery
No. of patients	20	20
Male	12	11
Female	8	9
Age range (yr)	21-77	23-73
Mean	46 ± 15	47 ± 16
Psoriasis severity (%)	20-60	20-65
Mean	32.8 ± 9.2	34.5 ± 7.6
Skin types	I-III	I-III
Mean	2.6 ± 0.7	2.3 ± 0.7

Clinical grading of psoriatic severity

Patients were examined and their psoriasis was graded before treatment and after 6 weeks of PUVA therapy—or earlier if clearance or maximum improvement was achieved. The grading system included an estimation of the percentage of skin involvement with psoriasis. In addition, erythema, scaling, and thickness of the psoriasis lesions were visually graded on a scale of 0 to 3: 0 indicated cleared disease; 1, mild disease on the lesions; 2, moderate disease on the lesions; and 3, the most severe signs of the disease on the lesions.

The clinical appearance of the lesions was ranked according to this grading system. The scale for erythema was as follows: 0 = no erythema; 1 = mild erythema; 2 = moderate erythema; and 3 = marked or severe erythema. For the scaling, the grading was as follows: 0 = no scale; 1 = mild or thin scale; 2 = moderate, usually adherent scale; and 3 = very thick, adherent scale. For thickness, the scale was as follows: 0 = no elevated psoriasis level with surrounding skin; 1 = slightly elevated; 2 = moderately elevated psoriasis; and 3 = extremely elevated or thickened psoriasis.

Clinical responses to either form of therapy were ranked as follows: clear = complete absence of skin disease; good improvement = less than 5% remaining psoriasis, with total erythema, scaling, and thickness scores of less than 3; and failed therapy = more than 20% remaining psoriasis, with total erythema, scaling, and thickness scores of 3 or greater.

8-Methoxypsoralen bath treatment

Treatment details. 8-Methoxypsoralen was stored in a 1% stock solution. Final bath solutions were prepared by diluting 30 ml of the 8-methoxypsoralen in 80 liters of body-temperature bath water, resulting in a final concentration of 3.75 mg/liter. Patients soaked for 15 minutes in the diluted bath solution and then quickly wiped dry. Immediately, patients were given whole-

Table II. Side effects seen in patients treated with 8-methoxypsoralen plus ultraviolet A delivered either orally or by bath-water

	No. of patients		
	Pruritus	Erythema	Nausea
Oral (n = 20)	2	4	6
Bath (n = 20)	3	7*	0

*Asymptomatic in five patients and occurred after the fifth 8-methoxypsoralen bath and ultraviolet A treatment. Cleared by 48 to 72 hours following PUVA treatment.

body irradiation with ultraviolet A according to skin types I to III. Skin types are defined as follows: I = always burns, never tans; II = always burns, then slightly tans; and III = sometimes burns, always tans. No patient with skin darker than skin type III was treated in this study. All treated patients wore ultraviolet A–absorbing, protective eyeglasses during their treatment.

Initial ultraviolet A doses were varied with skin type. Type I patients received 0.2 joule/cm^2, type II received 0.3 joule/cm^2, and type III received 0.5 joule/cm^2. Ultraviolet A exposures were given with an ultraviolet A machine composed of forty-eight vertical ultraviolet A tubes with a peak emittance of 365 nm. The ultraviolet A tubes emitted 13 to 16 mW/cm^2 of ultraviolet A radiation. The ultraviolet A machines were monitored continuously during therapy by measuring output and delivered ultraviolet A dose. Patients were treated two or three times weekly until clearance or until maximum disease improvement. The ultraviolet A was increased by half of the initial therapy (measured in joules per square centimeter) at each treatment (provided no phototoxic erythema was seen) to a maximum of 4 joules/cm^2.

Side effects of bath-water administration. Phototoxic effects of 8-methoxypsoralen baths and ultraviolet A were recorded as the appearance of erythema, itching, and worsening psoriasis.

Determinations of minimal phototoxic doses of 8-methoxypsoralen baths. Five volunteers participated in studies of minimal phototoxic doses to forearm skin exposed to 8-methoxypsoralen baths and ultraviolet A. A horizontal ultraviolet A therapy machine with the same spectral characteristics as the ultraviolet A machine was used for the bath studies (peak emission of 365 nm). This Elder portable local therapy ultraviolet A machine contained six 2-foot ultraviolet A tubes. One forearm of the test subjects was immersed for 15 minutes and the other for 30 minutes in the diluted bath solution of 8-methoxypsoralen. Determinations of minimal phototoxic doses were obtained after the first, third, and fifth forearm immersions in 8-methoxypsoralen bath water. The sites were read after 48 or 72 hours. The minimal phototoxic dose was measured as the minimum ultraviolet A dose causing definite erythema with well-defined margins.

Oral 8-methoxypsoralen treatment

Oral 8-methoxypsoralen was administered in a single dose of approximately 0.6 mg/kg and was provided in 10 mg capsules (methoxsalen) 2 hours prior to ultraviolet A exposure with the same ultraviolet A machines used for the 8-methoxypsoralen bath–treated patients. As before, initial ultraviolet A doses were varied with skin type. Type I patients received 1 joule/cm^2; type II patients received 2 joules/cm^2; and type III patients received 3 joules/cm^2. The patients were treated two or three times a week. The ultraviolet A was increased by half of the initial therapy (measured in joules per square centimeter) at each treatment (provided there was no phototoxic erythema) to a maximum of 15 joules/cm^2.

Side effects of oral 8-methoxypsoralen. Phototoxic and systemic effects of oral 8-methoxypsoralen and ultraviolet A exposure were recorded as nausea, erythema, itching, and worsening psoriasis.

Determinations of minimal phototoxic doses. Five psoriasis volunteers receiving oral 8-methoxypsoralen with ultraviolet A participated in the determinations of minimal phototoxic doses to the skin of the lower part of the back. Determinations were performed with the same technics as for the bath treatments, except that the ultraviolet A exposure was given 2 hours after the oral 8-methoxypsoralen dose (0.6 mg/kg body weight). The skin of the lower part of the back was exposed in 1-cm^2 areas to 5, 10, 15, and 20 joules/cm^2 of ultraviolet A. The minimal phototoxic dose was read at 48 hours after ultraviolet A exposure as the minimum ultraviolet A dose causing definite erythema with well-defined margins.

Monitoring of ultraviolet A

Throughout these studies the ultraviolet A machines were monitored with an IL500 radiometer with an attached broad-band ultraviolet A sensor head calibrated at 365 nm.

RESULTS

The results are also summarized in Tables II to IV.

Table III. Summary of treatment details for patients treated with either oral 8-methoxypsoralen or bath-water 8-methoxypsoralen (3.7 mg/liter)

	No. of patients			Total number of treatments (mean ± SD)	Final UVA (joules/cm²) (mean ± SD)	Total UVA (joules/cm²) (mean ± SD)
	Cleared	Good response	Failed therapy			
Oral delivery	8	8	4	19.3 ± 2.7	13.8 ± 2.1	191.1 ± 18.7
Bath-water delivery	8	9	3	13.1 ± 3.5	3.3 ± 1.6	29.9 ± 11.3

Table IV. Evaluation scores before and after the two different forms of 8-methoxypsoralen delivery and ultraviolet A therapy

	% body surface area	Erythema score	Scaling score	Thickening score
Oral 8-MOP + UVA (n = 20)				
Before therapy	35.0 ± 7.5	3.00 ± 0.00	2.84 ± 0.37	2.68 ± 0.48
After therapy*	7.9 ± 9.9	0.94 ± 0.77	0.47 ± 0.96	0.68 ± 0.82
8-MOP baths + UVA (n = 20)				
Before therapy	32.3 ± 9.1	2.90 ± 0.31	2.85 ± 0.37	2.85 ± 0.37
After therapy*	4.7 ± 3.74	0.65 ± 0.49	0.24 ± 0.43	0.47 ± 0.80

8-MOP: 8-Methoxypsoralen; UVA: ultraviolet A.
*All scored quantities are significantly decreased ($p < 0.005$) by therapy as revealed by Student's t test.

Oral PUVA

Eight patients had total clearing of all psoriatic plaques. Eight patients had good improvement in psoriatic lesions but did not have total clearing.

The average total number of joules per square centimeter used per patient was 191.1. The mean number of treatments to maximum improvement was nineteen. The mean number of joules per square centimeter at the final treatment was 13.8 ± 2.1 (Table III). Four patients had treatment failures. Three of these four patients stopped PUVA therapy on their own initiative. Of these, one had failed to improve and two had developed severe nausea.

The mean percent of body surface area involvement was 35.0 ± 7.5% prior to PUVA treatment and 7.9 ± 9.9% ($p < 0.005$) after treatment. The mean erythema score before treatment was 3.00 ± 0.00 and 0.94 ± 0.77 ($p < 0.005$) after treatment. The mean scaling score was 2.84 ± 0.37 before treatment and 0.47 ± 0.96 ($p < 0.005$) after treatment. The mean thickness score prior to treatment was 2.68 ± 0.48; after treatment, it was 0.68 ± 0.82 ($p < 0.005$) (Table IV). Side effects of nausea, pruritus, or erythema were seen and are summarized in Table II.

Table V. 8-Methoxypsoralen in bath water, yielding minimal phototoxic doses in normal volunteer forearm skin*

	Number of bath-water 8-MOP treatments		
	1 bath	3 baths	5 baths
MPD†	5.3 ± 0.6	3.8 ± 1.1	2.8 ± 0.3

8-MOP: 8-Methoxypsoralen; MPD: minimal phototoxic dose.
*Concentrations of psoralen were the same as for the bath-water delivery of 8-methoxypsoralen (3.7 mg/liter). Forearms were soaked in the solution for 15 minutes, dried, and ultraviolet A irradiation was then initiated.
†Expressed in joules per square centimeter ± SD.

Determinations of minimal phototoxic doses

With oral PUVA, the mean minimal phototoxic dose determination was 17.0 ± 1.9 joules/cm² af-

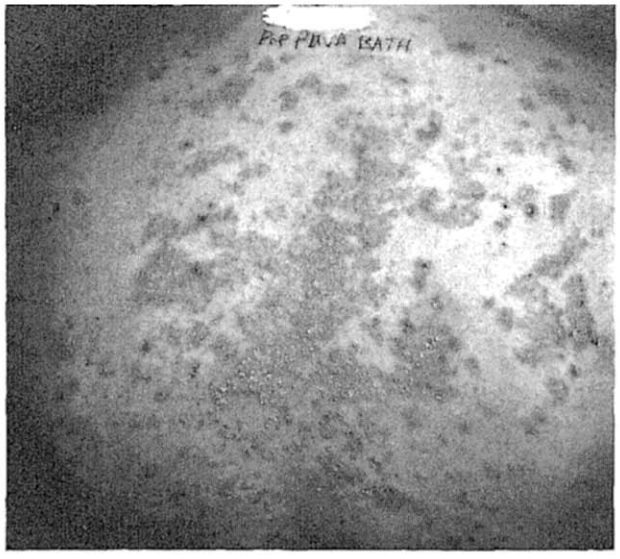

Fig. 1. The upper part of the back of a patient with psoriasis vulgaris before therapy.

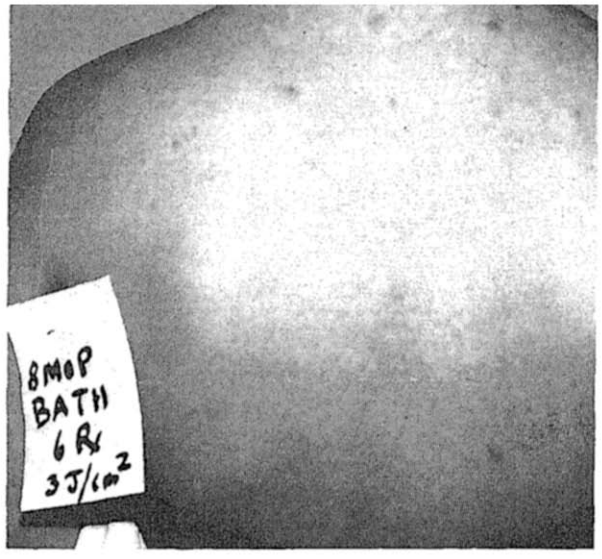

Fig. 2. The upper part of the back of the patient after the initial six treatments using 8-methoxypsoralen by bath-water delivery plus ultraviolet A. The remaining psoriasis on her legs cleared after a total of thirteen treatments and total ultraviolet A exposure of 28.2 joules/cm^2.

ter one dose. We are currently measuring minimal phototoxic doses after a greater number of treatments with oral 8-methoxypsoralen. Preliminary results suggest an increasing minimal phototoxic dose, suggesting skin protection perhaps resulting from pigmentation and epidermal thickening.

With psoralen bath therapy the mean minimal phototoxic dose was 5.3 ± 0.6 joules/cm^2 after one treatment (Table V). After three treatments the minimal phototoxic dose decreased to 3.8 ± 1.1 and after five treatments to 2.8 ± 0.3 joules/cm^2. Minimal phototoxic dose times decreased markedly from the first treatment to the last treatment ($p < 0.005$). We are currently measuring minimal phototoxic doses with greater numbers of treatments. It is likely that increased minimal phototoxic dose times occur with greater than five treatments, since most patients achieved final ultraviolet A exposure greater than 3 joules/cm^2 without developing phototoxic erythema.

Bath-water 8-methoxypsoralen treatment

Eight patients had total clearing of all psoriatic plaques. Nine patients had good improvement but did not have total clearing.

Psoralen bath therapy failed for three patients. One patient stopped topical psoralen administration because he did not like taking the baths. Two patients had phototoxic burns and stopped therapy. The phototoxicity symptoms resolved over 3 to 4 days.

The average total number of joules used per patient was 29.7 ± 11.3. The mean number of treatments to maximum improvement was thirteen. The mean number of joules per square centimeter at the final treatment was 3.3 ± 1.6 (Table III).

The mean percent of involved body surface area was 32.3 ± 9.1% prior to therapy and 4.70 ± 3.74% after therapy ($p < 0.005$). The mean erythema score prior to psoralen bath therapy was 2.90 ± 0.31 and 0.65 ± 0.49 after treatment ($p < 0.005$). The mean scaling score prior to bath therapy was 2.85 ± 0.37; after treatment, it was 0.24 ± 0.43 ($p < 0.005$). The mean thickness score was 2.85 ± 0.37 prior to therapy and 0.47 ± 0.8 after therapy ($p < 0.005$) (Table IV).

Figs. 1 and 2 show the back of a patient before and after six treatments with 8-methoxypsoralen bath plus ultraviolet A, respectively.

DISCUSSION

Oral 8-methoxypsoralen and ultraviolet A have been effectively used in the United States for treating psoriasis and other skin diseases.[1,2] The precise

mode of action of PUVA in psoriasis is still unknown. The most usual method of administration in the United States is oral 8-methoxypsoralen at a dose of 0.6 mg/kg, followed 2 hours later by ultraviolet A exposure. PUVA therapy has been shown to be beneficial in approximately 90% of treated patients, most of them within 6 to 12 weeks.[1] Recent studies suggest the erythema action spectra for 8-methoxypsoralen and 4,5′,8-trimethylpsoralen to be approximately 335 to 340 nm[8]; however, the action spectrum for the antipsoriatic effects of PUVA is currently not known. PUVA is also cost-effective in comparison with the Goeckerman regimen.

Topical application of psoralen with ultraviolet A light is also able to improve psoriasis[5,6] and has been suggested as an alternative to oral PUVA for localized psoriasis. A major advantage of topical treatment appears to be the absence of systemic side effects such as nausea and eye sensitization, reflected by the low serum levels of psoralen after bath-water delivery.[7] In addition, topical application produces high levels of skin 8-methoxypsoralen and thus the need for lesser amounts of ultraviolet A.[4] The methods of topical administration have included psoralens in a variety of lotion, cream, and ointment vehicles. A problem with topical 8-methoxypsoralen is that the application procedure is often laborious, and the treatment, as observed by one of us (N. J. L.), causes uneven, persistent pigmentation[5,6] and poorly controlled phototoxicity.

Another route of psoralen delivery is bath water. Studies of therapeutic effectiveness of psoralen baths suggest that the results are at least as good as with oral administration of psoralen, but no direct comparison has been reported. Bath-water psoralen delivery plus ultraviolet A has also been found to be equal to or better than local application of psoralens with ointment, creams, or lotions.[3] For example, trioxsalen bath delivery plus ultraviolet A therapy is reportedly effective in long-term maintenance treatment of psoriasis patients, yielding average remission rates of 4 months.[7]

There are several factors that make psoralen bath delivery easier for the patient than other topical psoralen treatments. Psoralen can be administered as a short, 15-minute bath. The baths eliminate the laborious application required with other topical modalities. Furthermore, the even skin distribution delivered by bath water leads to even pigmentation.

Common side effects (Table II) are primarily confined to immediate phototoxic reactions. Care has to be taken particularly with patients with skin type I. Of a more problematic nature is the potential skin carcinogenicity of PUVA therapy. An increase in nonmelanoma skin cancers in oral methoxsalen–treated patients has been reported.[9-12] Although topical psoralens and ultraviolet A are known to be carcinogenic to mouse skin,[13] one investigation failed to show an increased risk of skin cancer in patients with psoriasis who had been treated with psoralen baths and ultraviolet A.[7]

An important feature of psoralen baths is that penetration of bath-delivered psoralen into the bloodstream is markedly less than for oral psoralens,[14,15] perhaps thereby lowering the potential for systemic toxicity as evidenced by nausea or cataractogenesis.

The majority of the psoralen bath studies have used trioxsalen (4,5′,8-trimethylpsoralen),[3,7,15] which is ten to thirty times more photosensitizing than 8-methoxypsoralen and requires less ultraviolet A. Furthermore, 4,5′,8-trimethylpsoralen causes a longer-lasting erythema than 8-methoxypsoralen, peaking 5 days post exposure versus 2 days for 8-methoxypsoralen. This situation may favor the use of 8-methoxypsoralen to minimize unwanted phototoxicity.

It should be noted that our findings on the minimal phototoxic dose levels with the 15-minute 8-methoxypsoralen bath are significantly less than the previously reported findings of Koulu and Jansen.[4] We found a mean initial minimal phototoxic dose of 5.3 joules/cm^2, which fell to 2.8 joules/cm^2 after the fifth treatment. Koulu and Jansen found minimal phototoxic dose levels of 24 joules/cm^2 after the first treatment and 9 joules/cm^2 after the fifth treatment. This discrepancy can be explained by the effective concentration of psoralen in the bath water. Koulu and Jansen used a dose of 0.4 mg/liter, whereas we used 3.7 mg/liter. Additional studies are needed to determine whether 8-methoxypsoralen blood levels are significantly higher with the 8-methoxypsoralen bath-water concentration used in this regimen.

It should be emphasized that both oral delivery

and bath-water delivery of 8-methoxypsoralen, in combination with subphototoxic ultraviolet A radiation, improve psoriasis. However, visible cutaneous phototoxicity is an unwanted effect. Notwithstanding, the final ultraviolet A exposure for these patients was below their respective minimal phototoxic dose levels. These results demonstrate that visible cutaneous phototoxicity can be readily controlled with the use of bath-water delivery of 8-methoxypsoralen, provided that ultraviolet A irradiance is maintained at sufficiently low, yet therapeutically effective, levels.

Further studies are needed on the persistence in the skin of bath-water delivered 8-methoxypsoralen, particularly in lieu of the higher bath-water psoralen concentrations used in our regimen. Our patients were advised against sunbathing during the course of this study; however, it is likely that the dorsal aspect of the hands was exposed to both the 8-methoxypsoralen bath and sunlight. Although no occurrences of sun-induced phototoxicity were seen, it is prudent to advise sun protection of patients undergoing any frequent form of PUVA therapy.

In summary, treatment with 8-methoxypsoralen delivered by bath water plus the use of ultraviolet A is an effective alternative to oral 8-methoxypsoralen plus ultraviolet A for the treatment of psoriasis. Long-term follow-up is needed to determine relative skin toxicity and carcinogenic risk.

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