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TRIOXSALEN BATH PLUS UVA TREATMENT OF PSORIASIS

Plasma Concentration of the Drug and Clinical Results

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Abstract. Forty-five patients with psoriasis were treated with trioxsalen bath plus UVA. Good or excellent results were obtained in 34 (67%) of the 51 treatments. Trioxsalen plasma concentrations were determined at different stages of the treatment in 10 patients 1 hour after trioxsalen bath, and in 11 patients undergoing treatment for vitiligo 2 hours after ingestion of 0.6 mg trioxsalen per kilogram body weight. The determinations were performed using the glass capillary, gas chromatography, mass spectrometry method, reaching a sensitivity of ≥25 pg/ml. The trioxsalen plasma concentrations varied between 12.5 and 0.27 ng/ml after oral ingestion and between ~9 ng/ml and less than 25 pg/ml after bath application.

Key words: Psoriasis treatment; Trioxsalen; Plasma concentration

The PUVA method is widely used in the treatment of psoriasis. The necessary photosensitization of the skin is most commonly achieved with oral 8-methoxypsoralen (8-MOP) but local 8-MOP or trioxsalen baths are also used. Trioxsalen bath combined with UVA was demonstrated to be an effective treatment for psoriasis, by Fisher & Alsins (2) and by Hannuksela & Karvonen (5). The pharmakokinetics of 8-MOP after local application has been thoroughly studied (6), but little is yet known about trioxsalen (3).

It is evident that the peak of photosensitivity coincides with the maximum plasma concentration of 8-MOP (10). Oral administration of trioxsalen leads to weak photosensitization (7) and to very low plasma concentrations (3). We have studied the effect of trioxsalen bath plus UVA on refractory psoriasis and plasma concentration of trioxsalen after bath photosensitization in psoriatic patients.

MATERIAL AND METHODS

Forty-five patients with psoriasis were selected for the study at the Department of Dermatology, University Central Hospital, Helsinki. Twenty-six were males and 19 were females. The mean age of the 45 patients was 43.4 years, ranging between 17 and 76 years and the mean duration of psoriasis was 18.4 years, ranging between 1 and 43 years. Nineteen of the patients had earlier been treated with oral 8-MOP and UVA. The previous PUVA treatment had led to good or excellent results in 10 cases and had been ineffective or discontinued for various reasons in 9 cases.

The bath treatment was performed by bathing the patients for 10 min in 150 litres of water to which 50 mg of trioxsalen in alcoholic solution had been added. Within a few minutes after the bath the patients were exposed to UVA, starting from 0.2 J/cm² and reaching a maximum of 2 J/cm² per treatment session.

Blood samples for the determination of trioxsalen plasma concentrations were drawn from 10 patients 1 hour after the bath at different stages of the treatment. For comparison, blood samples were also drawn from 11 patients undergoing PUVA treatment for vitiligo 2 hours after ingestion of 0.6 mg trioxsalen/kg body weight.

Trioxsalen was determined in plasma samples using the method described by Taskinen et al. (11). The procedure involves extraction of trioxsalen and deuterium-labelled internal standard with dichloromethane, purification of extracts by high pressure liquid chromatography and quantitation by glass capillary gas chromatography mass spectrometry. Sensitivity of the method was 25 pg/ml. Precision, as measured by analysing replicate spiked samples, was 6% (c.v., $n=5$) at the level 100 pg/ml.

RESULTS

The clinical results of trioxsalen bath plus UVA treatment correlated with the results of earlier 8-MOP + UVA (PUVA) are presented in Table I.

A good or excellent clinical result was achieved in 34 (67%) of the 51 treatments. The mean number of Joules/cm² needed to achieve this result was 19.4, the range varying from 4.5 to 66 J/cm². In the patients with a poor result the mean number of Joules required in the treatment was 41.8, ranging between 7 and 190 J. The treatment had to be stop-

Table I. *The results of 51 trioxsalen bath + UVA treatments in 45 patients with psoriasis*

Patient group	No. of treatments with different results			
	Total	Good result	Poor result	Stopped
No previous PUVA	27	16	6	5
Good result in PUVA	13	11	1	1
Poor result in PUVA	11	7	3	1
Total	51	34	10	7

ped for various reasons in 7 patients, usually intense burning or irritation of the skin even with light doses of 0.2–0.4 J/cm².

Patients who had had poor results in the previous 8-MOP plus UVA treatment responded as well as those with good result in the previous PUVA treatment.

Table II presents the trioxsalen plasma concentrations obtained at different stages of the treatment. There is a wide variation in the plasma concentrations between individual patients and at different stages of the treatment. In only 5 patients were concentrations of ≥1 ng/ml achieved in the beginning of the treatment. The highest concentration obtained was ~9 ng/ml. The sensitivity of the method reaches 25 pg/ml and with progressing treatment, concentrations lower than 25 pg/ml were obtained in 6 patients.

The plasma concentrations after ingestion of trioxsalen by vitiligo patients are presented in Table III. The concentrations found are about 10 to 100 times higher than those after bath treatment.

DISCUSSION

The majority of the patients treated with trioxsalen bath plus UVA were selected from the patients in whom peroral 8-MOP and UVA could not be used for various reasons. In some of them 8-MOP and UVA had previously been tried without success. The good result in most of these cases may be attributable to the effective photosensitization achieved by bath application of trioxsalen. The effectiveness of the photosensitization is also reflected in the low mean total amount of light—19.4 J/cm²—needed to achieve the clearing of psoriatic lesions in the successful cases.

As far as side effects of the PUVA treatment are concerned, the usual side effect of peroral 8-MOP and UVA—nausea—was not seen and pruritus seemed to be less evident with trioxsalen bath and UVA. In the mouse, light *per se* (1) and 8-MOP + UVA (4) cause changes in the dermal connective tissue, but trioxsalen and UVA treatment do not appear to induce detectable changes in the collagen metabolism of the skin (14). With trioxsalen and UVA, this effect on the connective tissue should at

Table II. *Trioxsalen plasma concentration 1 h after bath*

Patient	Sample date	Concentration
B.-S.	01.09.78	1.9 ng/ml
	08.01.79	300 pg/ml
	30.01.79	110 pg/ml
P. T.	22.01.79	200 pg/ml
	14.02.79	<25 pg/ml
	20.03.79	100 pg/ml
K. M.	05.02.79	1.9. ng/ml
M. K.	01.02.79	760 pg/ml
	02.03.79	80 pg/ml
	30.03.79	<25 pg/ml
Po. T.	22.01.79	890 pg/ml
	14.02.79	<25 pg/ml
	26.03.79	880 pg/ml
K. Mz.	30.11.78	1.1 ng/ml
	03.01.79	50 pg/ml
	07.02.79	50 pg/ml
A. H.	14.12.78	660 pg/ml
	30.01.79	<25 pg/ml
R. L.	17.01.79	1.0 ng/ml
	16.02.79	110 pg/ml
	21.03.79	<25 pg/ml
S. L.	28.12.78	1.5 ng/ml
	24.01.79	~5 ng/ml
	26.02.79	~9 ng/ml
J. M.	04.12.78	2.3 ng/ml
	11.01.79	<25 pg/ml
	07.02.79	<25 pg/ml
S. R.	14.12.78	370 pg/ml

Table III. *Trioxsalen plasma concentration in patients with vitiligo 2 h after ingestion of ~0.6 mg/kg*

Patient	Trioxsalen concentration (ng/ml)
1	8.8
2	2.4
3	0.58
4	1.3
5	3.0
6	1.4
7	12.5
8	0.48
9	0.27
10	3.7
11	1.4

least be much weaker, both because of the lower amount of light and because of the low tissue concentration of trioxsalen in the dermis.

According to Kammerau et al. (6) application of a 1% ointment of 8-MOP applied to half the body surface gave the same absorbed amount as the oral administration of 0.5 mg/kg body weight. Usually the plasma levels of 8-MOP 2 hours after oral application of 0.5 mg/kg body weight vary between 900 and 2 ng/ml (8, 12, 13). After oral application of 0.6 mg trioxsalen/kg body weight the plasma concentrations varied between 0.27 and 12.5 ng/ml. The wide variation corresponds to that obtained with 8-MOP.

The plasma concentrations of trioxsalen after bath application are very low. The highest concentrations in most of the patients just reach the lowest values of 8-MOP or trioxsalen after oral application. However, after bath treatment the plasma concentrations are in general 10 to 1 000 times lower than those after oral ingestion of the drug.

The glass capillary, gas chromatography, mass spectrometry method used for the determination of trioxsalen plasma concentrations is extremely sensitive, reaching a level of 25 pg/ml and has a very good reproducibility. It is also highly specific, detecting trioxsalen only, but not its metabolites. The results of the present determination of trioxsalen plasma concentrations accord with the findings of Fischer et al. (3) who found in only 2 of their 4 patients a concentration of ≥2 ng/ml after bath treatment. About half of the present values are well below this value. In more than half of our patients the plasma concentrations of trioxsalen decreased during the progress of the bath treatment. This is possibly attributable to a decreased penetration through healing skin compared with that through untreated psoriatic skin. The low concentration of trioxsalen in the plasma and most probably also in the dermis combined with the small amount of light energy needed should lead to a diminished effect on the dermal tissue.

There are reports indicating an increased risk of skin cancer in certain groups of psoriatic patients treated with peroral 8-MOP + UVA (9). If the risk of developing cancer correlates with the effect of the treatment on psoriasis, then there should be no difference in this risk between the two treatment forms. There is however, one decisive difference in the tissue concentrations of the photosensitizing drug between the two treatment modalities. The concentration of perorally applied 8-MOP most probably decreases from the dermis to the epidermal surface, whereas the concentration of locally applied trioxsalen decreases from surface to dermis (15). The concentration difference on the dermal level is probably about 100-fold if there is a straight correlation between dermal and plasma levels. This assumption would appear to indicate that on the basal cell level, trioxsalen is either a far more potent photosensitizer than 8-MOP, or the effect of PUVA treatment on psoriasis is not entirely dependent on the inhibition of DNA synthesis by basal cells, but there exists some other mechanism by which the clinical effect is achieved at a higher level than in the basal cells.

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