

PHOTOCHEMOTHERAPY OF PSORIASIS WITH RELEVANCE TO 8-METHOXYPSORALEN PLASMA LEVEL AND LOW INTENSITY IRRADIATION

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Abstract. The 8-methoxypsoralen (8-MOP) plasma level was determined in 31 patients during treatment with PUVA (psoralen+UVA light). The UVA light source was of a low intensity type, giving only 2 mW/sec/cm² and required an irradiation time of 30 minutes. The lesions of 19 patients healed completely. Following an oral dose regimen adjusted to the patient's weight, the 8-MOP values at 2 hours varied from 2 ng/ml to 167 ng/ml (mean 56 ng/ml). There was no clearcut relation between the 8-MOP plasma level and the clinical response but in 9 patients there was a prompt response to treatment when the dose of psoralen was increased by 10 mg. In 5 patients the 8-MOP plasma levels was determined hourly for the first 4 hours and showed a peak at 2 hours except in one patient with very low values who had a peak at 4 hours. The augmentation of pigmentation was measured by means of reflectometry on three uninvolved areas. Two peaks were observed—one during the first week and the other after 2-3 weeks of therapy.

Key words: 8-Methoxypsoralen; Plasma concentration; Ultraviolet light; Psoriasis

Several reports describe the benefits of photochemotherapy with 8-methoxypsoralen (8-MOP) and longwave ultraviolet light (UVA) in psoriasis (4, 7, 10, 14, 15). This therapy effectively inhibits the increased DNA synthesis of the epidermal cells and produces regression of the psoriatic plaques, as in conventional topical therapy (12). It is cosmetically more acceptable and will presumably be widely used in the near future, provided there are no serious side effects. In this connection, the question of mutagenic effects on cells in the epidermis and dermis is of great importance. Not only are epidermal cells affected, but some cytogenetic studies have demonstrated chromosome aberrations in human lymphocytes (9, 10, 11) and induction of DNA repair synthesis in human fibroblasts (1). A combined in vitro/in vivo study by Swanbeck et al. (10)

demonstrated that these changes are related to the dosage of 8-MOP and light energy. Individual variations were described, both in clinical response to treatment, and in the frequency of chromosome aberrations. These variations may be due to inherent individual differences in response at a cellular level, but also to variations in concentration of the active substance in the skin. Thus theoretically the plasma level of 8-MOP could constitute a measure for the assessing of dose regimens and for predicting mutagenic effects. In this study we estimated the 8-MOP plasma levels in a group of psoriatic patients being treated with PUVA (psoralen+UVA). We also measured the augmentation of melanin pigmentation by means of reflectometry.

MATERIAL AND METHODS

In a preliminary study 13 patients aged 22 to 58 years (weight 52 to 87 kg) were treated with a low dose level of the psoralen 8-MOP, viz. 20 to 30 mg. The psoralen was supplied as 10 mg tablets by Nyco, W. Nyegaard & Co, Oslo (produced on licence from Memphis Chemical, Cairo, Egypt). Radiation with UVA was performed 2 to 2½ hours after ingestion of the psoralen. The purpose of this preliminary study was to determine the possible effect of a low dosage level, as this might have some bearing on consequent side effects and help in establishing a correct dose regimen.

In the subsequent study, 31 patients (including the original 13) were treated with recommended doses of 8-MOP, related to the patients' weight: 30-50 kg weight: 20 mg 8-MOP; 51-65 kg: 30 mg 8-MOP; 66-80 kg: 40 mg 8-MOP; 81-90 kg: 50 mg 8-MOP, and above 90 kg: 60 mg 8-MOP. All patients had extensive psoriatic lesions of long duration covering at least 50% of the body surface. Cases of acute exudative types of psoriasis and of severe heart failure or liver disease were excluded. Those patients previously treated with cytostatics or prednisone had to abandon this therapy for at least one month. Fourteen of

the patients were hospitalized, but after healing, all received ambulatory maintenance therapy. The following general blood tests were performed before and during the therapy: Hb, ESR, white blood cell count, blood platelets, alkaline phosphatase, SGOT, SGPT, and gamma-glutamyltranspeptidase (g-GT).

The stand-up light source was built up of 30 122 cm 40 W and 30 61 cm 20 W Philips black light lamps mounted to a height of 182 cm on 3 panels (10 rows of lamps on each) giving an almost total body irradiation with an effect of about 2 mW/cm²/sec on the body surface at a distance of 30–40 cm. The treatment schedule was as follows: The first exposures to UVA light were given daily increments of 5 min starting with 10 min (=1.2 J/cm²) and ending with 30 min (=3.6 J/cm²) as maximal exposure time. All subsequent exposures were of 30 min duration unless skin irritation occurred, in which case the dose was lowered. As a rule, all patients were irradiated 4–5 times a week until satisfactory healing of lesions was effected. They were then started on maintenance therapy which varied from twice weekly to once every second week.

The plasma concentration of 8-MOP was determined by means of high-pressure liquid chromatography with ethylic acetate extract of a plasma sample after evaporation and resolution in CHCl₃. Four ml of plasma was necessary to achieve an estimation accuracy of 2 ng/ml. Standard deviation was about 2–3% in the present study. The method has been described in detail by Jacobsen & Madsen (5). Blood for plasma determinations was withdrawn at the time of irradiation.

The increase in pigmentation was measured by a photoelectric reflection meter (Photovolt 670) on the first day of treatment and subsequently at weekly intervals. On a complete white glass surface this instrument reflected 82% of the light passed through a green filter (Tree-green). With increasing pigmentation of the skin, less light is reflected than from non-pigmented skin. Measurements were performed on uninvolved skin on (1) the left shoulder (2) volar aspect of the left upper extremity (l.u.extr.) and (3) left buttock.

The evaluation of the clinical response to PUVA therapy was graded as follows: excellent result (complete clearing of lesions), very good (between 80% and 100% clearing) good (50% to 80% clearing), fair (less than 50% clearing).

RESULTS

In the preliminary low-dose study, 5/13 patients were completely cleared of lesions after 11–43 (mean 14) treatment sessions, i.e. generally a total dose of less than 45 J. Four patients were 50 to 90% cleared, while 4 others were classified as failures, i.e. there was no response to therapy. When the dose of 8-MOP was increased according to the patient's weight, a 100% clearing was obtained even in the remaining 8 patients.

Table I shows the 8-MOP plasma levels, clinical responses, and numbers of treatment sessions in

patients on full-dose therapy. Surprisingly large variations in plasma concentration of 8-MOP, viz. from 2–167 ng/ml (mean 56 ng/ml), were observed from one individual to another. Very low values were observed in 6 patients: B. A., 3 ng/ml; R. A., 8 ng/ml; A. M., 5 ng/ml; R. R., 11 ng/ml; H. B., 11 ng/ml, and H. N., 2 ng/ml. In 3 patients the 8-MOP plasma level was more than doubled when the per oral dose was increased by 10–20 mg according to the full-dose regimen. A clear relation between plasma level of 8-MOP and clinical effect was not observed except in the patient B. A., who had 3 ng/ml. This patient reacted promptly when the dose was increased from 40 mg to 50 mg, i.e. 10 mg more than the schedule. The large number of treatments required was frequently due to many interruptions

Table I. Plasma levels of 8-MOP, clinical response, and numbers of treatment sessions with PUVA (*n*=31)

*=not on full dose; **=several interruptions; °=on maintenance treatment; °°=drop-out

Patient	Age (y.)	8-MOP (ng/ml)	Clinical response	No. of treatment sessions
F. K. ♂	35	108	Excellent	8°
A. M. ♀	45	5.2*	Excellent	46***
A. S. ♂	22	62	Excellent	25°
H. B. ♂	44	11	Excellent	28
E. S. ♂	40	167	Excellent	14°
A. M. ♀	40	44	Excellent	9°
E. F. ♀	58	105	Excellent	21°
S. E. ♀	28	70	Excellent	20°
J. L. ♂	28	73	Excellent	48°
J. G. ♂	48	123	Excellent	10°
R. R. ♂	55	19	Excellent	15
T. J. ♂	25	47	Excellent	34°
A. N. ♀	64	31	Excellent	65***
T. B. ♂	54	74	Very good (Excel.)	40***
L. O. ♂	48	57	Very good	12
R. A. ♀	54	8	Very good	7°
T. T. ♀	55	53	Very good	11***
B. G. ♀	38	18	Very good	20°
R. R. ♀	37	11	Very good	9
H. N. ♂	20	2	Very good	15°
F. R. ♀	22	67	Very good	25**
K. B. ♂	44	58	Very good	35**
V. G. ♀	27	28	Very good	37°
H. A. ♂	32	34	Very good	48**
S. B. ♂	59	25	Good	25**
B. A. ♀	42	3	Good	8
F. E. ♀	54	130	Good°	23
T. A. ♂	41	88.40*	Fair°	20**
O. S. ♂	45	43.10*	Fair°	20**
H. J. ♂	68	110	Fair°	31**
R. V. ♂	24	63	°°	2

Table II. Plasma turnover of 8-MOP in 5 patients during treatment with PUVA

Patient	Age (y.)	Plasma level of 8-MOP (ng/ml)			
		1 hr	2 hrs	3 hrs	4 hrs
L. O. ♂	48	39	57	44	24
F. K. ♂	35	94	108	84	70
B. A. ♀	42	2	3	2	2
R. A. ♀	54	2	8	8	2
A. M. ♀	45	2	2	2	5

in the therapeutic regime. Generally there was no excellent response before 15 to 20 treatments, although 2 patients were completely free of lesions after 8 to 10 treatments, respectively. A total of 13 patients were completely cleared after 8 to 65 treatments (mean 26). The plasma level of 8-MOP in these patients varied from 5 ng/ml to 167 ng/ml (mean 66.5 ng/ml). In 10 patients the results were registered as very good, i.e. 90–100% healing, after 7–48 treatments. The 8-MOP plasma level in these patients varied from 2 ng/ml to 74 ng/ml (mean 43.2 ng/ml). Three patients had a good response after 8–25 treatments, while the 8-MOP plasma level varied from 3 ng/ml to 130 ng/ml. Three other patients had only a fair response, with less than 50% clearing despite high plasma levels. Two of these patients (T. A. and O. S.) dropped out because of alcohol abuse, while another (H. J.) dropped out after 31 treatments. They had all had several interruptions in the therapy. The patient R. V. dropped out after just a few treatments.

Seventeen patients have been on maintenance therapy for 1 to 3 months and are still 90–100% clear of lesions. Two further patients have been entirely clear for 6 months without therapy. The remainder of the patients have dropped out or have not resumed the therapy on recurrence. The main reason for this was that the ambulant therapy was too time consuming, i.e. involved long journeys.

Table II shows the plasma turnover of 8-MOP during 4 hours in 5 patients after oral intake. Four of these patients had a very good to excellent response to PUVA therapy, while the fifth patient had about 50% clearing of lesions after 8 treatments. In 3 patients, the 8-MOP levels were extremely low, viz. about 2 ng/ml after 1 hour and 3, 8, and 2 ng/ml respectively after 2 hours. In one, the highest value (5 ng/ml) was observed after 4 hours, while in the others the peak level declined from 57 ng/ml and

108 ng/ml at 2 hours to 44 ng/ml and 84 ng/ml, respectively, at 3 hours.

Reflectometry

Table III shows the results of the measurements during PUVA therapy in 10 patients. On the first day of treatment the highest reflectometric values, i.e. the mildest pigmentation, were observed on the volar aspect of the l.u.extr. The lowest values, i.e. stronger pigmentation, were observed on the left shoulder. During the course of the therapy a gradual decrease in percentage reflection was observed. The total decrease after more than 20 treatments was 13.1% on the l.u.extr., 10.9% on the left buttock and 9.1% on the left shoulder. It was apparent that the change in reflection was greatest during the first 6 treatments, i.e. during the first week, and from 12 to 20 treatments, i.e. after 2 to 3 weeks.

Side effects

Two patients experienced localized erythema while a third patient got almost generalized erythema with a burning sensation of the skin. A pustular reaction was observed in one patient and a Koebner phenomenon with new psoriatic lesions on the buttocks was provoked in another patient. All patients could continue with the treatment after the UVA dose was reduced to 10 min, i.e. from approximately 1.8 J to 600 mJ. Four patients had a generalized pruritus which subsided during therapy, while 6 patients experienced nausea and a general feeling of weakness and fatigue. The nausea disappeared when the tablets were taken together with a light meal but the other symptoms persisted.

Table III. Reflectometry measurements during treatment with PUVA (n=10)

Time	Percentage reflection (mean values)		
	L. shoulder	L.u. extr.	L. buttock
(a) at 1st treatment	29.6	34.8	31.0
(b) At 6th treatment	26.5	29.5	24.3
(c) At 12th treatment	25.5	28.9	23.7
(d) At 20th treatment	20.5	21.6	20.1
Difference a-b	3.1	5.3	6.7
b-c	1.0	0.6	0.6
c-d	5.0	7.3	3.6
a-d	9.1	13.1	10.9

Some unawaited effects, which may be ascribed to the therapy, were bettering of nail symptoms in 3 patients, while the arthropathy was also seemingly less disabling in 2 patients.

General blood tests

These were normal in all patients except one, both before and during the therapy. This patient (J. G.) had pathological liver function tests, including a g-GT of 2000 U/L (normally <27 U/L). The pathological values were ascribed to daily use of ethyl alcohol. He was told to stop or diminish this during the therapy and the g-GT value 2 months later was 59 U/L, while the alkaline phosphatase, GOT, and GPT values were normalized.

DISCUSSION

The preliminary study clearly showed that some patients (in our investigation 5/13) may achieve acceptable results on low-dose therapy with PUVA. This concerns both the psoralen dose and the amount of UVA energy. The consequence of low-dose therapy is a delay in the clearing of the lesions. With regard to lifelong treatment, this problem would seem to be less important particularly if the risk of developing side effects can be diminished. From a practical point of view, high-intensity irradiation with short exposure times combined with the smallest possible yet still effective dose of psoralen would be preferable. Presumably this problem can be approached by measurement of the 8-MOP concentration in both blood and tissue, as there is a possibility that these two parameters are not in strict mutual correspondence. Accordingly, and because of the extremely large interindividual variations in 8-MOP plasma levels, concomitant determinations of the concentration in the skin (in particular the epidermis) would be of the greatest interest. The variations mentioned may also be of consequence for the disparity in frequency of chromosomal aberrations observed in lymphocytes during PUVA therapy (10).

Despite a prompt improvement following increased dose regimen in 8/13 patients in the preliminary study and in one patient (B. A.) on recommended doses, there was no clearcut relationship between 8-MOP plasma level, clinical response, and the number of treatments. One factor is the interindividual difference in DNA responsiveness. For instance the patient F. E. who achieved only

about 50% clearing of lesions despite 23 continuous treatments and a very high 8-MOP plasma level (130 ng/ml). This patient must accordingly be classified as a poor responder. On the other hand several patients obtained excellent results despite very low plasma concentrations and these patients are either good responders and/or have higher psoralen levels in the epidermis. Concerning possible variations in 8-MOP plasma levels from time to time in response to the same dose, these have been shown to be very small (5).

Wide variations, i.e. from 2–3 $\mu\text{g}\%$ up to 74 $\mu\text{g}\%$, have recently been reported by Wilkinson & Farber (13) using another method. No correlation between serum level and therapeutic response in individual patients was observed in their study either. Current investigations indicate that the dissolution rate of the substance may affect the plasma level and its time course markedly (2, 5). Whether this will be of consequence for the therapeutic response remains to be seen. In the present study the concentration peak occurred at 2 hours, as illustrated in Table II, and generally this is the right moment for irradiation. This accords with the findings of Pathak et al. (6). On the whole the 8-MOP plasma determinations indicated that several investigators have used relatively too large concentrations of psoralen in their *in vitro* studies.

The reflectometry observations indicate that the augmentation of psoralen pigmentation occurred mainly in two peaks, one during the first week and the second at about the third week of the treatment. Although the reason for this is not quite clear, it is related to immediate pigment darkening and the process of melanogenesis (3, 8). The gradual increase in the UVA dose may be responsible and the observations are partly in agreement with the reflectometric studies of Daniels et al. (3). The first peak may also represent the additional effect of vasodilation induced by the therapy, as green filter reflection includes both hemoglobin and melanin (3).

No hepatotoxic effect was observed during this study. On the contrary, the g-GT values, which are extremely sensitive parameters for the hepatocellular function, decreased during PUVA therapy in one patient who stopped or reduced his alcohol consumption.

Despite the time-consuming ambulant therapy which was sometimes hampered by interruptions, 17/31 patients were kept 90–100% clear of lesions

on maintenance therapy, while 2 more patients were entirely cleared without need for any further treatment. Three patients were classified as failures. Accordingly, although a not-insignificant number of patients improved on this therapy, the results are somewhat poorer than those obtained with high intensity irradiation, and the need for such equipment is supported. Individual responsiveness to PUVA on the cellular level seems to be an important factor and may call for a flexible assessment of the psoralen dose regimen.

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