

## PLASMA LEVELS OF 8-METHOXYPsorALEN AND PHOTOTOXICITY STUDIES DURING PUVA TREATMENT OF PSORIASIS WITH MELADININ TABLETS

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**Abstract.** A new tablet formulation of 8-methoxypsoralen was used in PUVA treatment for psoriasis. The 8-MOP plasma level showed a maximum at about 1 hour after ingestion (mean values:  $\frac{1}{2}$  hr, 284  $\mu\text{g/l}$ ; 1 hr, 275  $\mu\text{g/l}$ ;  $1\frac{1}{2}$  hr, 198  $\mu\text{g/l}$ ; 2 hrs, 129  $\mu\text{g/l}$ ). Phototoxicity tests showed the optimal time for exposure to be about 1 hour after peroral intake of 8-MOP.

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

Photochemotherapy for psoriasis based on the synergistic action of 8-methoxypsoralen (8-MOP) administered perorally plus long-wave ultraviolet light (UVA) irradiation, has been shown to be very successful and presumably harmless (7). The effect is associated with DNA-psoralen photoproducts and interstrand DNA cross-links. These reactions are confined to areas penetrated and reached by UVA, viz. the skin. In vitro studies indicate that the photochemical reaction is dependent upon both the UVA dosis and the psoralen concentration (5).

A method for the assessment of 8-MOP concentration in plasma has been described by Jacobsen & Madsen (1). Based on this method we recently described the effect of PUVA (psoralen+UVA) in relation to the 8-MOP plasma level (3). Large variations in 8-MOP concentration were observed, viz. between  $<2$  and 167  $\mu\text{g/l}$  (mean 52.5  $\mu\text{g/l}$ ).

This report deals with the results obtained with a new tablet formulation of 8-MOP which produces much higher plasma levels than could be obtained with the original (8-MOP) tablet.

### MATERIAL AND METHODS

Eight patients, 4 women and 4 men, aged 37 to 73 years were investigated. All of them suffered from extensive

psoriatic eruption of chronic type located on the trunk and all extremities. They were treated with recommended oral doses of 8-MOP, related to the patient's weight (mean 0.52-0.63 mg/kg).

The 10 mg tablets were of a new formula (supplied by Nyegaard & Co. A/S, Oslo) and given 1 hour prior to UVA irradiation ("Black light"). The light source was the same as described previously (3): Philips Black Light lamps mounted at a height of 182 cm on 3 panels (10 rows of lamps on each), giving an almost total body irradiation with a peak at 365 nm. The output was approximately 2 mW/cm<sup>2</sup>. The treatment schedule was as follows: the patients were exposed 3-5 times a week, starting with 10 min (=1.2 J/cm<sup>2</sup>). The exposure time was gradually increased by 5 min; after about 8 treatments all patients were receiving 30 min exposures (=3.6 J/cm<sup>2</sup>). The evaluation of the clinical response to PUVA therapy was graded as follows: 100% clearing (complete disappearance of erythema and scaling), 80-100% clearing, 60-80% clearing, 40-60% clearing, etc. Blood samples for 8-MOP determination were withdrawn  $\frac{1}{2}$  hour, 1 hour,  $1\frac{1}{2}$  hours and 2 hours following ingestion of the tablets. The plasma concentration level was determined by means of high pressure liquid chromatography and a 254 nm UV detector as described by Jacobsen & Madsen (1). The lowest limit of detection is 2  $\mu\text{g/l}$ .

In order to evaluate the time relationship between 8-MOP medication and irradiation on the induction of phototoxicity, 6 patients were irradiated on the back 0 min, 20 min, 40 min, 60 min and 120 min after ingestion of a tablet. The irradiation was performed with a Xenon XBO 150 W lamp equipped with appropriate Schott filters for the production of UVA radiation (KG 1+WG 320+UG5 filter combination). The distance from the lamp to the patient's skin was 20 cm and the mean output was 720 mW/cm<sup>2</sup> as measured by a Hewlett & Packard Radiant Flux Meter. Each test area (10 mm diameter on the back), received a total dose of 10.8 J/cm<sup>2</sup>.

### RESULTS

Six out of 8 patients became entirely free of lesions after 15 to 29 treatments. Two patients were 80-100% cleared.

Table I. Plasma concentrations (in  $\mu\text{g/l}$ ) of 8-MOP at various time intervals after oral intake

n.d. = Not done

Patient	Plasma concentration of 8-MOP			
	$\frac{1}{2}$ hour	1 hour	1½ hour	2 hours
P. H. ♂	470	200	150	80
A. O. ♀	70	230	130	110
A. H. ♂	380	n.d.	440	220
R. M. ♀	550	320	180	110
O. J. ♂	430	530	280	220
P. N. ♀	87	337	131	70
A. L. ♂	n.d.	114	158	86
				(32 after 3 hours)
M. S. ♀	<3	197	117	72
Mean values	284	275	198	129

The plasma concentration levels of 8-MOP after oral intake are illustrated in Table I. The highest mean value was actually obtained at  $\frac{1}{2}$  hour (284  $\mu\text{g/l}$ ) but was only slightly lower at 1 hour (275  $\mu\text{g/l}$ ). Two patients, P. H. and R. M., had much higher values at  $\frac{1}{2}$  hour (470  $\mu\text{g/l}$  and 550  $\mu\text{g/l}$ , respectively), than at 1 hour (200  $\mu\text{g/l}$  and 320  $\mu\text{g/l}$ , respectively).

Table II illustrates the results of the phototoxicity tests. The time relationship between dose and exposure indicates that the 1 hour interval seems to be optimal, but reactions were evoked both before and after 1 hour. Most of the reactions were observed 48 hours after irradiation, but in 2 patients 72 hours elapsed before reactions occurred. Generally speaking, the reactions were stronger at 72 hours than at 48 hours. In one case a 3+ reaction occurred, i.e. erythema with oedema and vesiculation.

### DISCUSSION

The present investigation indicated that appropriate 8-MOP plasma concentrations can be achieved at about 1 hour and that optimal phototoxicity is also produced at that time. Other investigations referring to another type of 8-MOP have indicated an optimal time of 2 hours (2, 7). The new formula used in this study apparently produced a more rapid absorption and diffusion into the skin. These results may be of greatest significance for the therapy and may imply that some ambulatory patients can take the medication while in hospital. Curiously, the same exposure doses had to be used

Table II. Results of phototoxicity tests performed at various time intervals after oral intake of 8-MOP in 6 patients

Exposure dose of UVA: 10.8 J/cm<sup>2</sup>

Time after 8-MOP intake (min)	No. of positive reactions at		
	24 hours	48 hours	72 hours
0	—	—	—
20	—	1	—
40	1	3	2
60	2	4	4
120	2	3	3

in these patients as in those previously studied (3) although the present patients had much higher 8-MOP plasma concentrations.

It certainly seems to be of importance to establish the optimal level of 8-MOP in the blood. So far, only two other studies have dealt with assays for 8-MOP after per oral intake. Wilkinson & Farber (6) reported a range of 2.3–7.4  $\mu\text{g}\%$  in 31 patients, while Steiner et al. (4) found mean values to be 0.58  $\mu\text{g/ml}$ . Despite the fact that various types of tablets and methods of analysis have been used, the results accord with those obtained in the present study. For most patients the values reported may be optimal but this does not exclude that a lower 8-MOP dosage also may be sufficient (2). Although poor responses to PUVA therapy cannot consistently be related to low plasma levels of 8-MOP, there is a tendency for more patients to respond satisfactorily when high plasma levels are induced.

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