DIFFERENCE IN BIOAVAILABILITY BETWEEN TWO BRANDS OF 8-METHOXYPSORALEN AND ITS IMPACT ON THE CLINICAL RESPONSE IN PSORIATIC PATIENTS

MARJA J. HERFST¹* & FREDERIK A. DE WOLFF²

¹Department of Dermatology and ²Laboratory of Toxicology, University Hospital, 2333 AA Leiden, The Netherlands

1 Several 8-methoxypsoralen (8-MOP) preparations are now available for photochemotherapy of psoriasis. To assess differences in clinical response two preparations marketed in The Netherlands, Oxsoralen® capsules (Elder) and Meladinine® tablets (Basotherm), were given to eight psoriatic patients. Serum concentrations and the minimal phototoxic dose (MPD) as a measure for clinical response were determined.

2 Bioavailability and serum peak concentrations were significantly higher for Meladinine in all patients and the MPD value favoured Meladinine in 5 of the 8 patients. The mean time of the serum peak concentrations was 1 h earlier for Meladinine than for Oxsoralen.

3 These findings are relevant not only for the choice of drug in individual patients but also for comparison of the results of multicentre trials performed in different parts of the world.

Introduction

In The Netherlands several brands of 8-methoxypsoralen (8-MOP) were recently introduced for the PUVA photochemotherapy (irradiation of psoriatic patients with long-wave ultraviolet light (UVA) 2 h after 8-methoxypsoralen ingestion). Two of them, Oxsoralen® capsules (Ox) produced by P.B. Elder Co. (U.S.A.) and Meladinine® tablets (Me) manufactured by Basotherm GmbH (W. Germany), are compared in this study. Both preparations contain 10 mg 8-MOP.

When our department started to use PUVA therapy in 1975, a difference in clinical effect was found between 8-MOP (Sigma) and Me in favour of the latter (Polano & Schothorst, 1977). Other investigators (Busch *et al.*, 1978; Thune, 1978; Kreuter & Higuchi, 1979; Andersen *et al.*, 1980; Ljunggren *et al.*, 1980; Stolk *et al.*, 1980) also found differences in bioavailability between other oral administration forms. Since the therapeutic effect of 8-MOP may, therefore, be strongly dependent on the form in which it is administered, we studied the bioavailability and the clinical effect of Ox and Me in psoriatic patients.

Methods

Eight psoriatic patients who were to start PUVA therapy agreed to participate in the following experiment. Like all other PUVA patients, they started with the initial therapy, i.e., 3 irradiations a week. During the first month, Ox was used therapeutically in a dose of 0.5–0.6 mg/kg body weight. In this period two psoriasis-free areas on the buttocks were covered during irradiation to permit determination of the minimal phototoxic dose (MPD) on the two days on which the experiment was to be performed one month later. The MPD is the minimal dose of UVA (J/cm²) which causes in combination with a standard dose of 8-MOP (0.5–0.6 mg/kg body weight) a minimal perceptible erythema. The MPD is determined by irradiating 2 × 2-cm template squares on the buttocks with increasing doses of UVA energy, ranging from 1.5 to 9 J/cm², 2 h after ingestion of the standard 8-MOP dose (Wolff *et al.*, 1977). The degree of erythema is read 3 days after irradiation by two independent experienced investigators. Neither the therapeutic dose of UVA nor 8-MOP produces any erythema when given alone.

On one of the two test days, Ox (charge no. 79G31) was administered at 08.30 h on an empty stomach together with 50 ml water and a slice of bread with marmalade. Before 8-MOP was administered, a

*Present address: Diaconessenhuis, Houtlaan 55 2334 CK Leiden, The Netherlands

Table 1 Individual 8-MOP serum concentrations (ng/ml) and areas under the curve (ng ml⁻¹ h)

Patient	Schedule Ox/Me ^a	Group A/B ^b	Time (h)												AUC ^c
			0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5		
1	Ox	A	0	158	215	272	293	246	252	179	154	122	94	199	
	Me		0	420	542	467	360	262	234	176	126	102	80	277	
2	Ox	A	0	9 ^d	9	35	38	80	92	144	126	88	89	71	
	Me		0	287	280	270	270	198	179	150	122	92	66	191	
3	Ox	B	0	9	9	9	18	32	34	29	24	19	17	20	
	Me		0	130	98	75	51	29	23	22	20	17	14	48	
4	Ox	A	0	9	9	11	9	9	9	9	9	9	9	9	
	Me		0	10	163	148	127	49	35	21	12	23	11	60	
5	Ox	B	0	9	9	9	30	41	19	22	11	9	9	17	
	Me		0	9	38	52	58	35	33	19	14	9	9	28	
6	Ox	B	0	9	38	78	110	70	51	30	14	9	9	42	
	Me		0	19	146	160	141	70	45	40	36	32	21	71	
7	Ox	B	0	0	60	52	38	26	23	11	10	9	9	24	
	Me		0	59	209	151	105	51	42	26	17	13	10	68	
8	Ox	A	0	15	9	9	9	9	19	20	23	14	22	15	
	Me		0	9	17	65	70	75	109	111	57	44	22	58	

^aOx = 8-MOP serum concentration after Oxsoralen intake

Me = 8-MOP serum concentration after meladinine intake

^bA/B = schedule order; A: first Ox, then Me; B: first Me, then Ox^cAUC = area under the curve^d9 = < 10 ng/ml

Maximum serum concentrations for each series are printed in italics.

Butterfly cannula was inserted into an arm vein. Just before 8-MOP ingestion and at 30 min intervals for 5 h after that, 5 ml blood was collected. The MPD test was performed 2 h after 8-MOP intake, after which PUVA treatment was applied. After UVA irradiation the patient ate two slices of bread and marmalade. Throughout the experiment fluid intake was free except for coffee, cocoa and milk or a milk product.

On the second test day, Me was given (charge no. 7004). The procedure was the same as for Ox administration.

The patients were randomly divided into two groups (A and B). Group A received Ox on the first test day and Me 3 days later; group B was treated in the reverse order. This interval was taken at 3 days because the MPD test was to be read after that time. Reading of the MPD tests were performed independently by two experienced observers, according to the criteria and scoring described by Wolff *et al.* (1977), i.e. 1 = minimal perceptible erythema, 2 = light-pink erythema, 3 = marked erythema, red in colour but no edema. During the week of the experiment only these two UVA treatments were given.

The 8-MOP serum concentrations were determined with the high-performance liquid chromatographic (h.p.l.c.) method published elsewhere (Herfst *et al.*, 1980).

The 8-MOP contents of the dosage forms were determined by chloroform extraction of either triturated tablets or the powder in the capsules and measurement of the extinction with an ultraviolet spectrophotometer at 313 nm.

The mean pharmacokinetic data for Ox and Me in the 8 patients are summarized in Table 2. It is clear that Me is more rapidly absorbed than Ox, and that the peak concentrations, the concentration at the time of UVA irradiation and the area under the curve are significantly higher for Me than for Ox.

Table 3 shows the MPD for the UVA dose (in J/cm²) at which it was barely perceptible after three days. Five out of eight patients had a more sensitive MPD test after intake of Me than after Ox; the other

Results

Table 1 shows the serum concentrations of 8-MOP during the 5 h after administration for Ox and Me. The peak values, which occurred between 0.5 and 4 h after drug intake, are italicized. The areas under the curve (AUC) between t = 0 and t = 5 are also given.

The mean pharmacokinetic data for Ox and Me in the 8 patients are summarized in Table 2. It is clear that Me is more rapidly absorbed than Ox, and that the peak concentrations, the concentration at the time of UVA irradiation and the area under the curve are significantly higher for Me than for Ox.

Table 3 shows the MPD for the UVA dose (in J/cm²) at which it was barely perceptible after three days. Five out of eight patients had a more sensitive MPD test after intake of Me than after Ox; the other

Table 2 Mean pharmacokinetic data for Ox and Me in eight patients

	Ox ¹	Me ¹	P ²
T _{max} (h)	2.4 (1.0–4.0)	1.4 (0.5–3.5)	0.013
C _{max} (ng/ml)	90 (11–293)	208 (58–542)	0.014
C _{2h} (ng/ml)	68 (9–293)	148 (51–360)	0.014
AUC (ng ml ⁻¹ h)	50 (9–199)	100 (28–277)	0.014

¹mean (range)²signed rank test (two sided)

three did not show any difference between the MPD tested after Ox or Me intake.

The mean 8-MOP content of the Ox capsules was 9.1 ± 0.61 (mean $\pm$ s.d., $n = 60$), that of the Me tablets 10.2 ± 0.22 ($n = 10$) ($P < 0.001$, two-sided t -test).

Discussion

For all patients tested, both the 8-MOP peak serum concentration, the concentration at the usual time of irradiation (2 h after drug ingestion) and the AUC are higher after Me intake than after Ox. Not only do the mean AUC of the two tests differ significantly but also the mean times of 8-MOP peak concentrations. C_{max} after Me intake usually occurs just before the time of irradiation; 8-MOP concentrations after Ox

ingestion are, generally speaking, maximal after UVA application has been performed. The MPD tests do not reflect this difference as strongly as would be expected from the above-mentioned pharmacokinetic differences, probably because measurement of the MPD is semi-quantitative and less discriminating than the assay of serum concentrations. It is, however, clear from Table 3 that five of the eight patients are more photosensitive after Me ingestion, and three have the same MPD value after Me and Ox.

The slower absorption and reduced bioavailability of Ox under standard conditions are most probably caused by differences in dosage form, crystalline size of 8-MOP and/or auxiliary substances (Busch *et al.*, 1978; Thune, 1978; Kreuter & Higuchi, 1979; Ljunggren *et al.*, 1980; Polano & Schothorst, 1980; Stolk *et al.*, 1980). More unlikely explanations are: accelerated metabolism, distribution, and/or elimina-

Table 3 The individual minimal phototoxic dose (MPD) registered after Oxsoralen®(Ox) and Meladinine®(Me) intake

Patient	Schedule Ox/Me	1.5	2	4	5	7	9 J/cm ²
1	Ox Me		1 ^a 1				
2	Ox Me			1	1		
3	Ox Me			1 1			
4	Ox Me			1			1
5	Ox Me			1		1	
6	Ox Me				1 2 ^b		
7	Ox Me		1	1			
8	Ox Me			1 1			

^a 1 = minimal perceptible erythema^b 2 = light pink erythema

tion of Ox. The average 8-MOP content of one Ox capsule is about 10% lower than that of one Me tablet, but this difference cannot account for the 100% differences in peak serum levels and AUC's.

Andersen *et al.* (1980) compared Oxsoralen® (Austrian brand) and Meladinine® (Danish brand) and found the opposite of the results presented here. The brands we used regrettably bear the same names, but are made by different companies in different countries.

These findings illustrate the difficulty involved in the comparison with the therapeutic results of multi-centre trials when different drug brands are used, for instance the PUVA European Clinical Trial

(Henseler *et al.*, 1981) in which both tablets and capsules were used and the PUVA Cooperative Clinical Trial in the U.S.A. (Melski *et al.*, 1977) when only Oxsoralen® (Elder) was used.

Thus, for the treatment of psoriatic patients it is of importance that a PUVA centre uses one 8-MOP preparation whose bioavailability and pharmacokinetics are known and whose quality is constant.

We thank Mr J.G.P. Tijssen (Dept. Medical Statistics) for his assistance in the statistical analysis, and Mr B. Broer for skilful technical assistance. Support for this study was provided by the Praeventiefonds grant no. 28-343a.

References

- ANDERSEN, K.E., MENNE, T., GAMMELTOFT, M., HJORTH, N., LARSEN, E. & SOLGAARD, P. (1980). Pharmacokinetic and clinical comparison of two 8-methoxypsoralen brands. *Arch. Dermatol. Res.*, **168**, 23-29.
- BUSCH, U., SCHMID, J., KOSS, F.W., ZIPP, H. & ZIMMER, A. (1978). Pharmacokinetics and metabolite-pattern of 8-methoxypsoralen in man following oral administration as compared to the pharmacokinetics in rat and dog. *Arch. Dermatol. Res.*, **262**, 255-265.
- HENSELER, T., HÖNIGSMANN, H., WOLFF, K. & CHRISTOPHERS, E. (1981). Oral 8-methoxypsoralen photochemotherapy of psoriasis. The European PUVA study: a cooperative study among 18 European centres. *Lancet*, **i**, 853-857.
- HERFST, M.J., EDELBROEK, P.M. & DE WOLFF, F.A. (1980). Determination of 8-methoxypsoralen in suction blister fluid and serum by high-performance liquid chromatography. *Clin. Chem.*, **26**, 1825-1828.
- KREUTER, J. & HIGUCHI, T. (1979). Improved delivery of methoxsalen. *J. pharm. Sci.*, **68**, 451-454.
- LJUNGGREN, B., CARTER, M., ALBERT, J. & REID, T. (1980). Plasma levels of 8-methoxypsoralen determined by high-pressure liquid chromatography in psoriatic patients ingesting drug from two manufacturers. *J. invest. Dermatol.*, **74**, 59-62.
- MELSKI, J.W., TANNENBAUM, L., PARRISH, J.A., FITZPATRICK, T.B., BLEICH, H. & 28 Participating Investigators (1977). Oral methoxsalen photochemotherapy for the treatment of psoriasis: A cooperative clinical trial. *J. invest. Dermatol.*, **68**, 328-335.
- POLANO, M.K. & SCHOTHORST, A.A. (1977). Difference in the efficiency of two delivery forms of 8-methoxypsoralen. *Dermatologica*, **154**, 216-218.
- STOLK, L., KAMMEYER, A., CORMANE, R.H. & VAN ZWIETEN, P.A. (1980). Serum levels of 8-methoxypsoralen: Two oral methods of administration. *Br. J. Dermatol.*, **103**, 417-420.
- THUNE, P. (1978). Plasma levels of 8-methoxypsoralen and phototoxicity studies during PUVA treatment of psoriasis with Meladinine tablets. *Acta Dermatovener.*, **58**, 149-151.
- WOLFF, K., GSCHNAIT, F., HÖNIGSMANN, H., KONRAD, K., PARRISH, J.A. & FITZPATRICK, T.B. (1977). Phototesting and dosimetry for photochemotherapy. *Br. J. Dermatol.*, **96**, 1-10.

(Received September 7, 1981)