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PHARMACOKINETIC COMPARISON OF SEVEN 8-METHOXYPSORALEN BRANDS

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Abstract. The pharmacokinetics of seven 8-MOP brands were evaluated in 7 volunteers using an incomplete bloc design. After a single oral dose the 8-MOP plasma level was followed for 3 hours. The plasma concentration was measured with a gas chromatographic – mass spectrometric method, using an isotopic dilution technique. The different brands could be divided into three groups. Two gave a high maximum concentration, four a medium, and one a low concentration. The large interbrand variation observed in this study can explain the variations in the results of the treatment and the differing numbers of joules required to clear the patients in various PUVA centers.

Key words: PUVA treatment; 8-MOP pharmacokinetics; Gas chromatography – mass spectrometry

The dose required in PUVA therapy to clear psoriasis varies in the literature from 12 to 247 J/cm² (3). The 8-methoxypsoralen (8-MOP) plasma level is an important variable in producing a given result of treatment: Wagner et al. (7) found a low 8-MOP plasma level in patients with an unsatisfactory response to PUVA treatment. Our patients needed an average of 190 J/cm² to clear their psoriasis; the maximum plasma concentration obtained with a Danish 8-MOP brand was 5.6 times lower than the 8-MOP brand used in Austria (1).

This study compared the pharmacokinetics of seven 8-MOP brands after oral administration.

MATERIALS AND METHODS

Seven 8-MOP brands were investigated (Table I). Seven healthy volunteers (weight 48–95 kg, age 25–38 years) received 8-MOP orally in a dose of 0.6 mg per kg. The Danish Meladinine® which has been found to give a low plasma concentration (1) was given in a double dose. All volunteers received three brands, at 1-week intervals, according to a randomized, balanced incomplete block design (2) advantageously reducing the number of experiments performed on the individual volunteer. The capsules/tablets were taken during fasting and no food was given during the following 3 hours of blood sampling. Blood was drawn every 30 min followed by immediate centrifugation. Using the isotopic dilution technique, 4-ml aliquots of plasma were mixed with 100 µl of a spike solution containing 1µg/ml of a standard of 8-MOP perdeuterated in the methoxy group. The spiked samples were stored at −20°C until analysis was performed using the extracting procedure of Ehrsson et al. (4), followed by our gas chromatographic – mass spectrometric method (GC–MS) described elsewhere (1). The 8-MOP content in the different brands was controlled by analysis of two capsules/tablets of each brand. Statistical methods include analysis of variance and Student's *t*-test.

RESULTS

The 8-MOP content in the preparations varied less than 5% from the stated content (cf. Table I). All 8-MOP plasma concentrations are shown in Table II. The order in which the brands were given to the volunteers is indicated in column 'Brand no.'. For each experiment the logarithm of the concentra-

Table I. *Content of 8-MOP in capsules/tablets nominally containing 10 mg 8-MOP from the seven different companies*

Brand name	Brand no.	8-MOP per capsule/tablet	
		mg	mg
Draco 1210® Swedish, tablet	5	10.0	9.9
Meladinine®, Basotherm German, tablet	6	10.0	9.9
Meladinine®, pHarma-medica Danish, tablet	7	9.9	9.9
Meladinine®, Promedica French, tablet	4	10.0	9.5
Methoxalen®, Westwood American, capsule	3	10.1	9.5
Oxsoralen®, Elder American, capsule	1	10.1	9.9
Oxsoralen®, Gerot Austrian, capsule	2	10.1	10.0

Table II. *Plasma levels of 8-MOP in 7 healthy volunteers after oral administration of different brands*

Person	Sex	Body weight (kg)	Dose (mg)	Brand no.	Plasma 8-MOP after intake (hours)[a] 0 h (ng/ml)	½ h (ng/ml)	1 h (ng/ml)	1½ h (ng/ml)	2 h (ng/ml)	2½ h (ng/ml)	3 h (ng/ml)	3½ h (ng/ml)
A	♂	89	50	4	5	15	126	144	73^{5}	56^{5}	39^{5}	
			50	1	9	13	109	113		54	41	
			50	2	0.7	0.6	0.5	4	8	157	146	
B	♂	89	50	1	0	0^{5}	125^{5}	255^{5}	189^{5}	171^{5}	134^{10}	
			50	5	0.4	3	340	385	505	432	314	
			50	6	0.4	1.5	343	240	204	193	174	
C	♂	70	40	3	7	2^{15}	10^{15}	4^{15}	3^{15}	12^{15}	14^{15}	
			80	7	0.4	10^{5}		110^{-5}	174^{-5}	134^{15}		
			40	1		4	1.3	3	5	12	22	
D	♀	60	30	4	1.4	0.4^{-10}	9^{-10}	65^{-10}	73^{-10}	75^{-10}	57^{-10}	
			30	6	4	11	25	17	15	8	7	
			30	3	0.8	2	5	10	20^{10}	17	16	
E	♀	60	30	2	1	1	2	26	32	14	15	
			30	5	6	68	151	82	37	21	17	
			30	3	1	5	16	19	16	8	11	
F	♀	57	30	4	3	8	8	6	47	44	27	
			30	5	1	11	107	103	62	38	19	
			60	7	5	31	41	84	89	65	55	
G	♀	58	30	6	10	93		181	158	142	121	95
			60	7	2	97	211	228	239	291	302	
			30	2	3	10	71	84	72	65	51	

[a] The index given by some of the values indicates how many minutes must be added to get the correct time after intake of 8-MOP.

tion was plotted versus time. The maximum concentration and the time for maximum concentration were determined (Tables III and IV). It was chosen to analyse the logarithm of the maximum concentration, because the plots indicated that the variation in the 8-MOP concentration was better suited to a log-transformation. The analysis of variance showed statistically significant ($P<0.05$) differences in maximum concentration between the seven brands. The mean values with 95% confidence limits are presented in Fig. 1. In accordance with *t*-tests, Fig. 1 describes the differences between the brands as follows: Brands 5 and 7 gave significantly ($P<0.05$) higher 8-MOP plasma concentrations than all the others (except no. 4). Brand 3 gave a significantly ($P<0.05$) lower concentration than the others (except nos. 1 and 2). Brands 1, 2, 4 and 6 showed no mutually significant differences ($P>0.05$). In this investigation brand 7 was given in a double dose as our recent study (1) would otherwise have predicted plasma concentrations which were too low—well below the maxima found for the other brands.

The analysis of variance of the time of the maximum concentration showed no statistically

Table III. *The plasma maximum concentration of 8-MOP*
The values are determined from the semilogarithmic curves based on the measurements given in Table II

Person	Brand, plasma max. conc. 1 (ng/ml)	2 (ng/ml)	3 (ng/ml)	4 (ng/ml)	5 (ng/ml)	6 (ng/ml)	7 (ng/ml)
A	115	157		145			
B	250				505	343	
C	22		14				174
D			20	78		25	
E		32	19		151		
F				47	110		90
G		85				181	302

Table IV. *The time for maximum concentration of 8-MOP in plasma*

The values are determined from the semilogarithmic curves based on the measurements given in Table II

	Brand, time for max. conc.						
Person	1 (min)	2 (min)	3 (min)	4 (min)	5 (min)	6 (min)	7 (min)
A	80	150		80			
B	100				100	60	
C	180		180				115
D			130	120		60	
E		120	90		60		
F				130	75		110
G		80				90	180

significant ($P>0.05$) differences between the brands. The mean values were scattered around 2 h but there was a tendency for brand 6 to reach its maximum earlier than the others.

DISCUSSION

The 8-MOP plasma level obtained after a single oral 8-MOP dose shows great individual variation (Wagner (7), Andersen (1), Steiner (6)), which cannot be related to the inconsistency in the 8-MOP content of the tablets as measured by Hensby (5).

The experimental design used in this trial divided seven 8-MOP preparations into three groups: two brands gave a high maximum concentration, four a medium, and one a low concentration. Danish Meladinine® (brand no. 7), given in a double dose, showed a peculiar behaviour. The expected low plasma concentration for a 0.6 mg/kg dose (1) rose to an unexpectedly high value in this investigation when 1.2 mg/kg was used, suggesting a possible dose-related absorption. Two earlier studies (Wagner (7), Steiner (6)) did not show any correlation between the 8-MOP dose and the plasma level obtained.

The results regarding time for maximum concentration showed ranges which might explain individual treatment failures, but also supported the present

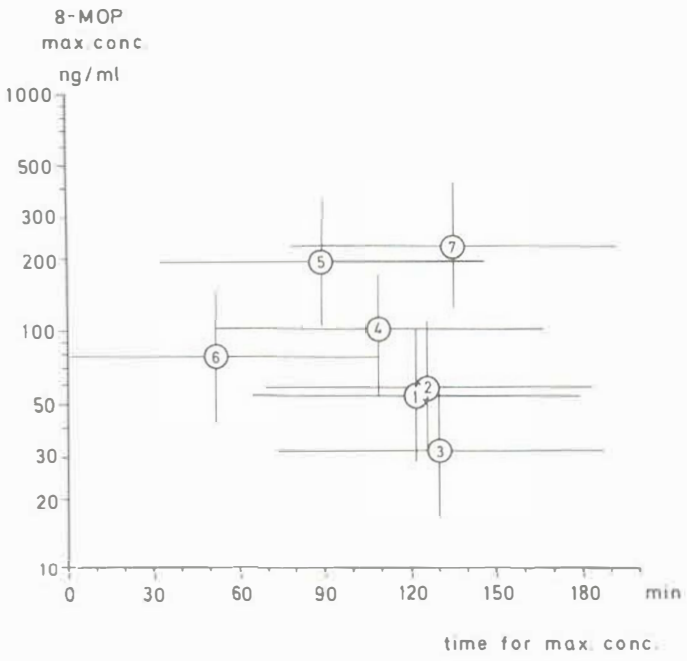

Fig. 1. The mean maximum plasma concentration and the mean time for maximum concentration with 95% limits are shown for the seven 8-MOP brands. The Danish Meladinine®, no. 7, was given in double dose.

routine of radiation 2 hours after tablet ingestion. In Wagner's study (7) 50 % of the problem patients and only 14 % of the controls had concentration maxima far removed from 2 hours.

In future comparisons of PUVA treatment, it will be necessary to give the specification of the 8-MOP preparation and the PUVA equipment used.

CONCLUSIONS

The large interbrand variation revealed by the present study accounts for the variations in the treatment results and the differing numbers of joules required to clear patients in the various PUVA centres.

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