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A New Micronized 5-Methoxypsoralen Preparation

Higher Bioavailability and Lower UVA Dose Requirement

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A new tablet of micronized 5-methoxypsoralen (5-MOP) and a commonly used tablet in therapy (Psoraderm 5®) were compared in 12 healthy subjects. Each subject ingested 1.2 mg/kg body weight of each formulation on different days. Bioavailability and phototoxicity of 5-MOP were compared. The results showed that serum and suction blister concentrations were significantly higher and occurred earlier after the oral intake of the micronized preparation. A series of graduated UVA doses were administered, one dose each time the concentration serum peaked, in order to determine the minimum phototoxic dose for each formulation. The micronized preparation induced greater photosensitivity than the unmicronized one. The micronized 5-MOP tablet may thus allow lower doses of UVA to achieve therapeutic results in photochemotherapy and a shortened waiting period following ingestion of drug. ***Key words: PUVA therapy; Pharmacokinetic; Micronized drug; Skin absorption.***

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Some authors (1,2) have introduced 5-Methoxypsoralen (5-MOP) as an alternative to 8-Methoxypsoralen (8-MOP) because of its less pronounced side effects, especially phototoxicity and nausea. Oral 5-MOP photochemotherapy is now a well established treatment for dermatological diseases such as psoriasis and vitiligo. The variability in absorption kinetics and bioactivity of the commonly used crystalline preparation (Psoraderm 5®) has been described elsewhere (3,4). Furthermore, previous studies have shown that the efficacy of PUVA therapy depends on the plasma psoralen concentrations (5,6).

In the present study, we administered micronized and unmicronized drug to 12 normal subjects on different days and compared 5-MOP bioavailability and phototoxicity. Serum levels, suction blister fluid levels and minimum phototoxic doses (MPD) of UVA were measured and compared.

MATERIAL AND METHODS

Volunteers

Twelve subjects were studied: 8 men and 4 women, with an age range from 23 to 55 years, weights ranging from 54 to 86 kg. All were healthy and taking no medication. Informed consent was obtained.

Drugs

Two different preparations of 5-MOP were tested. One was a new crystalline micronized drug tablet; the other was a commonly used crystalline unmicronized drug tablet (Psoraderm 5®). Each tablet contained 20 mg 5-MOP. Both preparations were supplied by Bergaderm Company (Rungis, France). Each volunteer ingested randomly 1.2 mg/kg body weight of 5-MOP of one of the preparations on the first test day of the experiment and the same dose of the other preparation on the second test day. The two test days were separated by at least 72 h. Just before taking the oral drug, a standardized low-lipid meal was taken by each subject.

Serum concentrations

Blood samples were obtained at 0, 0.5, 1, 1½, 3 and 7 h after the drug administration. The serum fractions were separated and stored at −20°C until assayed. Serum concentrations of 5-MOP were determined by high-performance liquid chromatography (HPLC) using a fluorimetric detector (7,8).

Suction blister fluid concentrations

During the serum pharmacokinetics, the cutaneous pharmacokinetics were performed in the following way: the interstitial fluid was collected using a suction blister technique (9). Two hours before the oral drug intake, corresponding to the time of blister formation, the suction blister device was applied on the volar aspect on the forearm with a vacuum of 350 mmHg. Three groups of 7 blisters were raised simultaneously. Four blisters were required for a single determination of 5-MOP. Suction blister fluid samples were taken at 0, 1, 1½, 3 and 7 h after the drug administration, using an insulin syringe. All the samples were stored at −20°C. Suction blister fluid concentrations of 5-MOP were determined using the same procedure as for the serum.

Ultraviolet source

The source of ultraviolet radiation was a Sun Well lamp with an irradiance of 35 mW/cm^2.

Exposure doses and procedure

The minimal phototoxicity dose (MPD) was determined at each subject plasma peak. Scapular and lumbar zones were randomly allocated for each MPD determination. Thus, on a test day, a series of 8 exposure doses was given either on the scapula or in the lumbar zone, according to the following procedure: eight test fields measuring 2 cm in diameter were irradiated with increasing UVA doses: 1½, 2, 3, 5, 7, 9, 11, 13 J/cm^2, the rest of the body being covered. Subject's phototypes were: III ($n = 3$); IV ($n = 7$); V ($n = 2$). Forty-eight hours after each UVA irradiation, the exposure sites were observed to determine the MPD as described in the literature (10).

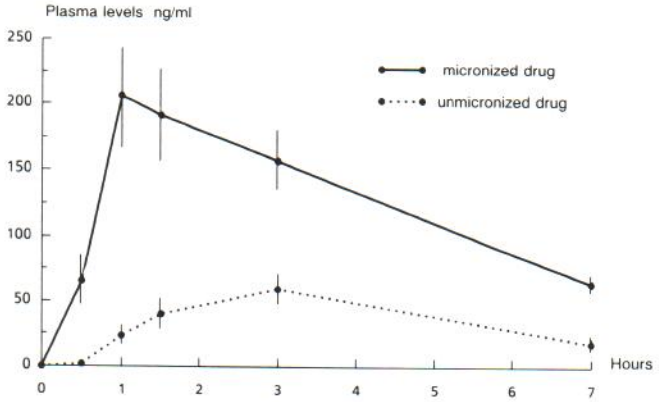

Fig. 1. Serum level profiles (mean ± S.E., $n = 12$) for micronized and unmicronized 5-MOP at 7 h.

Table I. *Mean ± S.D. serum pharmacokinetic parameters*

AUC, area under the curve; C_{max}, peak concentration; T_{max}, time of peak concentration

	Micronized drug	Unmicronized drug
AUC, ng.h/ml	890 ± 385	272 ± 140
C_{max}, ng/ml	249 ± 118	68 ± 38
T_{max}, h	1.45 ± 0.7	3.04 ± 1.4
Half-life, h	3.2	2.23

Statistical analysis

Pharmacokinetic parameters and MPD of micronized and unmicronized 5-MOP were compared using the non-parametric two-sided Wilcoxon rank sum test.

RESULTS

Plasma levels

Mean 5-MOP plasma levels after the oral intake of micronized and unmicronized drugs are presented in Fig. 1. Pharmacokinetic parameters are given in Table I. The area under the curve (AUC), the peak concentration (C_{max}) and the half-life were significantly higher with the micronized drug ($p < 0.01$). The mean AUC data indicated that micronized 5-MOP bioavailability was approximately three-fold greater than the commonly used 5-MOP. Time of peak concentrations (T_{max}) was reduced by half ($p < 0.01$). This demonstrates a faster rate of absorption of the micronized 5-MOP than with the unmicronized 5-MOP.

Suction blister fluid levels

Data are illustrated in Fig. 2. Cutaneous pharmacokinetic parameters are presented in Table II, differences between the two 5-MOP formulations being significant ($p < 0.05$). These results confirm the plasma pharmacokinetic parameters. When the unmicronized drug was administered, suction blister fluid levels at 1 and 1½ h were undetectable. Because of the very low drug concentrations, it was possible to determine 5-MOP suction blister fluid levels in only 5 subjects at 3 and 7 h. The micronized drug produced an AUC 8-fold greater than the unmicronized drug and a T_{max} less than half.

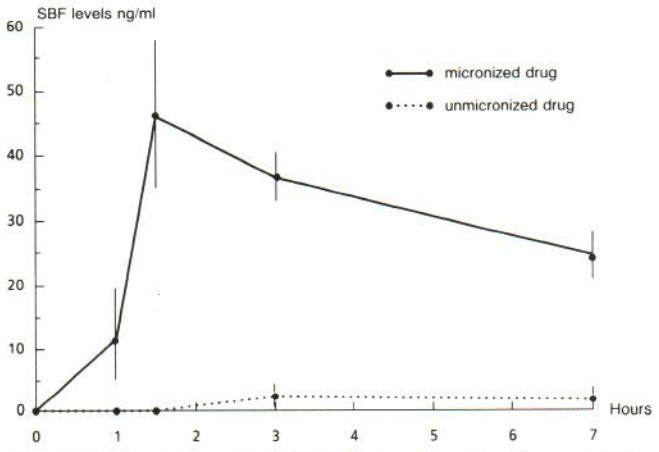

Fig. 2. Suction blister fluid (S.B.F.) level profiles (mean ± S.E., $n = 12$) for micronized and unmicronized 5-MOP at 7 h.

Table II. *Mean ± S.D. cutaneous pharmacokinetic parameters*

AUC, area under the curve; C_{max}, peak concentration; T_{max}, time of peak concentration

	Micronized drug	Unmicronized drug
AUC, ng.h/ml	242 ± 140	29.6 ± 22
C_{max}, ng/ml	60 ± 43	9.2 ± 4.5
T_{max}, h	2 ± 0.8	4.6 ± 1.9
Half-life, h	7.4	4

Photosensitivity (MPD)

All the individual data were gathered in Table III. The mean (± S.D.) of the MPD after the micronized drug was 8 ± 3.2 J/cm^2, and after the unmicronized drug, it was 12.7 ± 0.7 J/cm^2 ($p < 0.01$).

In 3 subjects (unmicronized drug) and 1 subject (micronized drug, the MPD were > 13 J/cm^2. The results were assigned to 13 J/cm^2 for statistical purposes.

Short-term side effects

Throughout the drug administration period, subjects were continuously monitored for subjective and objective signs of short-term side effects. No side effects such as erythema, blistering, pruritus or nausea were observed for either preparation. This is an important point, considering that micronized 5-MOP generates high plasma levels.

DISCUSSION

Because of its very poor water solubility, particle sizes of 5-MOP are an important parameter for dissolution and absorption. Smaller particles (micronized form of a drug) usually dissolve quicker, resulting in a better absorption.

Some reports have shown that 8-MOP bioavailability is

Table III. *Individual data obtained from micronized 5-MOP (A, B, C) and unmicronized 5-MOP (A′, B′, C′)*

A, A′: plasma peak concentrations (C_{max}, ng/ml)
B, B′: suction blister fluid peak concentrations (C_{max}, ng/ml; D.L., detection limit)
C, C′: M.P.D. (J/cm^2)

Subject	A	B	C	A′	B′	C′
1	179	32	7	28	<D.L.	13
2	292	132	5	54	<D.L.	13
3	270	106	5	56	<D.L.	>13
4	162	74	7	96	11	13
5	162	31	9	33	<D.L.	13
6	497	58	13	41	7	>13
7	423	28	7	25	<D.L.	13
8	328	137	5	55	3	11
9	185	39	7	139	15	11
10	242	23	5	132	10	13
11	143	20	13	97	<D.L.	13
12	111	38	>13	64	<D.L.	>13

higher when liquid or micronized preparations were administered (11–15). Concerning 5-MOP, Stolk et al. (16) and Tanew et al. (17) also showed that the bioavailability was better when the drug was micronized. Nevertheless, to our knowledge, no author has investigated 5-MOP cutaneous pharmacokinetic. A recent report (18) shows that suction blister fluid concentrations of 5-MOP were approximately three-fold higher when the blisters were raised during drug ingestion, compared with blisters raised 2 h before drug ingestion. In the present work, we raised the suction blisters 2 h before the oral drug intake, which probably reduced our suction blister fluid levels. Furthermore, from the micronized 5-MOP, suction blister fluid $T._{max}$ was obtained a halfhour later than the plasma $T._{max}$ and from the unmicronized 5-MOP, this interval was increased up to 1½ h. These results were not in agreement with previous work dealing with 8-MOP (15, 19), where plasma and suction blister fluid $T._{max}$ occurred simultaneously. The interval of 1½ h found between plasma and suction blister fluid peaks with the unmicronized drug demonstrates that it could be preferable to perform UVA irradiation at the moment of suction blister fluid peak. When we consider the ratios plasma $C._{max}$/ suction blister fluid $C._{max}$, they were 4 and 8 for the micronized and the unmicronized 5-MOP, respectively, and show very large interindividual variations (Table III).

The use of micronized 5-MOP in photochemotherapy has several advantages over unmicronized preparations: 1) it produces higher serum levels; 2) it peaks in the serum at 1.45 h, after ingestion and thus leads to a higher patient acceptance, as it reduces the waiting period between drug ingestion and treatment; 3) its cutaneous bioavailability is 8-fold greater; this demonstrates that micronized drugs penetrate much more easily into suction blister fluid; 4) it requires a smaller UVA radiant exposure to elicit photosensitivity reactions. The use of micronized 5-MOP should then allow us to optimize the PUVA therapy. It may be interesting in evaluating the micronized drug according to the 5-MOP chronopharmacokinetic recently published (20).

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