CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-969

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

D Catterson
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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	20,969
Submission Dates:	February 25, March 26, 1998, and January 06, 1999
Drug Name:	Uvadex (8-methoxypsoralen)
Formulation & Strength:	20 mcg/ml, sterile solution
Sponsor:	Therakos, Inc. 437 Creamery Way Exton, PA 19341
Reviewer:	N.A.M. Atiqur Rahman, Ph.D.
Type of Submission:	New Drug Application

SYNOPSIS

This review discusses the clinical pharmacology and biopharmaceutics related issues presented in the NDA submission by Therakos, Inc. in support of Uvadex Sterile Solution for use with the UVAR Photopheresis System. Uvadex is indicated in the palliative treatment of the skin manifestation of cutaneous T-cell Lymphoma (CTCL) in patients who have been unresponsive to other forms of treatment. No new pharmacokinetic studies have been conducted to support this NDA. The sponsor submitted published reports of the human pharmacokinetics and bioavailability of orally and intravenously administered Methoxsalen, active component of Uvadex sterile solution.

Methoxsalen is currently given orally two hours before photopheresis. The current treatment requires achieving a minimum of 50 ng/mL Methoxsalen blood concentration for effective treatment of CTCL patients. Uvadex will provide a concentration of 270 ng/mL of Methoxsalen in the photoactivation bag and subsequently to the 240 mL of leukocyte-enriched buffy coat. This procedure will avoid exposure variation associated with variable oral absorption of Methoxsalen.

The sponsor estimated an 86% reduction in the serum plasma levels of methoxsalen via the proposed route compared to the oral route of treatment. In the summary the sponsor also mentioned that the mean patient plasma level 30 minutes post-reinfusion of photoactivated buffy coat was 22.6 ng/mL. Reanalysis of the data by the reviewer shows that the mean concentrations of Methoxsalen 30 minutes post-reinfusion on treatment day 1 and treatment day 2 were 34.3 and 28 ng/mL, respectively. Therefore, Uvadex provides lower systemic exposure to Methoxsalen compared to orally administered Methoxsalen currently used for treatment of CTCL patients.

BACKGROUND

Methoxsalen (8-methoxypsoralen) is a member of the group of compounds known as psoralens or furocoumarins. Methoxsalen is a naturally occurring compound that is present in many plants, including food plants such as citrus, parsley, celery and figs. The pharmaceutical product available in the United States is a synthetic compound with the chemical name 9-methoxy-7H-furo(3,2-g)(1)bezopyran-7-one. Methoxsalen is a photosensitizing agent, which preferentially accumulates in epidermal cells. Methoxsalen is usually used in combination with ultraviolet light activation, a treatment known as PUVA (psoralen plus ultraviolet light A). Upon photoactivation, Methoxsalen forms covalent bonds with DNA in the nucleated cells leading to the inhibition of DNA synthesis, cell division, and cell viability over several days.

Methoxsalen (8-MOP, ICN; NDAs 09-048, 19-660) is approved in the United States for oral use in the treatment of severe, recalcitrant psoriasis, for repigmentation of idiopathic vitiligo, and for the treatment of skin manifestations of cutaneous T-cell lymphoma (CTCL). Treatment of psoriasis and vitiligo are approved as PUVA (psoralen plus ultraviolet light A). Treatment of CTCL is currently approved under a Premarket Approval Application (PMA P860003) as photopheresis. Photopheresis is the collection and exposure of extracorporeally circulating leukocyte-enriched blood to long-wave ultraviolet (UVA) energy in the presence of the photoactive drug.

UVADEX is developed for extracorporeal use in conjunction with the UVAR photopheresis system. This new dosage form should permit the delivery of a standardized concentration of Methoxsalen directly to the extracorporeal blood volume. Systemic exposure to Methoxsalen will be reduced, thus reducing or potentially eliminating the side effects of nausea and sunlight sensitivity. UVADEX sterile solution is indicated for use with the UVAR Photopheresis System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma in patients who have been unresponsive to other forms of treatment.

Item 6 (Human Pharmacokinetics and Biopharmaceutics Section) of the NDA contains 11 publications, five of which are listed in the **Appendix**. These five studies evaluated the pharmacokinetics and metabolism of Methoxsalen. One of these studies investigated the pharmacokinetics and distribution of Methoxsalen following intravenous administration. The other four studies compared the pharmacokinetics and distribution of Methoxsalen following administration as tablets, capsules, or oral solutions. One study compared tissue levels of Methoxsalen to those determined in plasma.

UVAR Photopheresis Procedure

The phases of a photopheresis treatment with the UVAR Photopreresis System include the following steps.

(a) Collection of leukocyte-enriched blood: In six cycles of blood withdrawal, whole blood is centrifuged and separated. In each cycle of separation plasma (volume determined by the operator) and buffy coat (40mL) are saved. The red cells and all additional plasma are reinfused to the patient before beginning the next collection cycle. In the six collection phases, 300mL of plasma and 240mL of buffy coat are collected.

(b) Photoactivation: The photoactivation of the leukocyte-enriched blood within the photoactivation circuit begins during the buffy coal collection of the first collection cycle. 10mL of Uvadex (20 μg/mL) is injected directly into the photoactivation bag during the buffy coat collection in the first cycle. At the end of six cycles, 200 μg of psoralen is mixed with 740mL of total volume (300mL of plasma, 240mL of buffy coat, and 200 mL of saline) providing psoralen concentration of 270 ng/mL in the photoactivation bag. After the specified 740mL are reached in the bag, photoactivation continues for an additional 1.5 hours of UVA irradiation.

(c) Reinfusion: Following the photoactivation period, the total volume is reinfused by gravity. Recommended time for the reinfusion of the leukocyte-enriched blood is 30 to 45 minutes.

Current Procedure

Methoxsalen is currently approved for oral use in the treatment of severe, recalcitrant psoriasis, for repigmentation of idiopathic vitiligo, and for the palliative treatment of skin manifestations of cutaneous T-cell lymphomas (CTCL). Treatment of CTCL is approved under a Premarket Approval Application (PMA P860003) as photopheresis. In the treatment of CTCL, Methoxsalen is ingested orally two hours before photopheresis. The recommended oral dose is 0.6 mg /kg. Extracorporeally circulating leukocyte-enriched blood is exposed to long-wave ultraviolet (UVA) radiation. Upon photoactivation, the leukocyte-enriched blood is reinfused in the systemic circulation.

Advantage of the Proposed Procedure

The effectiveness of the photopheresis for CTCL depends upon achieving a minimum effective blood concentration of at least 50 ng/mL following oral administration of Methoxsalen. High inter-subject and intra-subject variability after oral administration result in unpredictable exposure of the leukocytes to the drug which in turn may

compromise with the effectiveness of the therapy. However, this is not proven. The peak plasma concentrations in 18 psoriatic patients after oral administration of 0.6 mg/kg methoxsalen ranged from 41 to 319 ng/mL on day 1 of the treatment. Uvadex treatment of leukocyte-enriched buffy coat reduces differential exposure due to highly variable Methoxsalen oral pharmacokinetics. Systemic exposure to Methoxsalen is reduced avoiding toxicity associated with oral administration of the drug.

Pharmacokinetic Studies

No new pharmacokinetic studies have been conducted to support this new drug application. The sponsor has provided published reports of the human pharmacokinetics and bioavailability of orally and intravenously administered Methoxsalen. The minimum blood concentration of methoxsalen for effective photopheresis is 50 ng/mL. The mean plasma level of methoxsalen after oral methoxsalen administration at the recommended dose in CTCL patients was 102 ng/mL, with a maximum level of 327 ng/mL. Methoxsalen levels in the photoactivation bag obtained during the clinical trial had a mean concentration of 203 ng/mL. The sponsor in the March 26, 1998 Amendment to the original NDA submission mentioned that 754 (30 minutes post-reinfusion) serum samples were evaluated for levels of Methoxsalen. The mean Uvadex level for these serum samples was 22.6 ng/mL. The reviewer reanalyzed the data. Seventeen percent (67/397) and 18% (65/364) of the samples analyzed for Treatment Day 1 and Treatment Day 2 had detectable levels of methoxsalen. The average serum methoxsalen concentrations on Day 1 and Day 2 were 38.4 and 28.0 ng/mL in samples with detectable levels. The validated assay had a lower limit of quantitation of 10 ng/mL. Therefore, Uvadex provides minimum systemic exposure to methoxsalen likely reducing the systemic toxicity associated with the oral administration of methoxsalen.

Labeling Comments

1. On page 2, first paragraph in the "Clinical Pharmacology" section, the statement

Should be **replaced** as follows:

Interpatient variability is high; however, the cited paper does not specify the 18-fold difference in inter-patient variability as stated in the label by the sponsor. Reviewer's assessment shows a 6 to 15 fold interpatient variability in peak plasma concentration in a cited article titled " Intraindividual and interindividual variability in 8-methoxypsoralen kinetics and effect in psoriatic patients" published in Clin. Pharmacol. Ther., July, 1983.

2. On page 3, the last paragraph in the "Clinical Pharmacology" section, the statement

Should be **replaced** with the following statement,

The statement is based on the information provided in the NDA submission (Vol. 1.11, page 000194).

Recommendation

This review supports the approval of the NDA from the Clinical Pharmacology and Biopharmaceutics perspective. The Clinical Pharmacology and Biopharmaceutics information provided in the NDA submission fulfils the requirement of the Office of Clinical Pharmacology and Biopharmaceutics. The labeling comments should be incorporated in the package insert.

/S/ 2/11/99

Atiqur Rahman, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation I

/S/ 2/11/99

Mehul U. Mehta, Ph.D.
Acting Division Director
Division of Pharmaceutical Evaluation I

CC:

NDA 20969	original
HFD-150	Division File
HFD-150	DCatterson
HFD-150	IChico
HFD-850	LLesko
HFD-860	MMehta, ARahman, JDuan
CDR	Barbara Murphy

APPENDIX 1

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pages of trade

secret and/or

confidential

commercial

information

APPENDIX 2

Intraindividual and interindividual variability in 8-methoxypsoralen kinetics and effect in psoriatic patients

Our purpose was to investigate the origin of intraindividual variation in comparison with interindividual variation of 8-methoxypsoralen (8-MOP) kinetics in different body fluids. The clinical test in therapy with psoralens and ultraviolet A (PUVA), expressed as the minimal phototoxic dose (MPD), was performed to establish a possible connection between biologic effect and kinetics of 8-MOP. The MPD and 8-MOP kinetics in serum and suction blister fluid (sbf) were determined in 18 psoriatic patients on PUVA therapy in 4 test days spread over a 7-mo period. Evidence showed that interindividual fluctuations are caused by differences in intrinsic clearance (Cl). Interindividual variations are large in comparison with intraindividual variations. A correlation was found among maximal serum concentrations, Cls, MPDs, and concentrations in sbf. In clinical practice the maximal serum concentration, determined in blood samples taken at 1, 2, and 3 hr after 8-MOP ingestion, is indicative of the rate of 8-MOP metabolism and thus of the biologic effect in the patient.

Marja J. Herfst, M.D., and Frederik A. De Wolff, Ph.D. *Leiden, The Netherlands*
Department of Dermatology and Laboratory of Toxicology, University Hospital

Therapy with psoralens and ultraviolet A (PUVA), i.e., irradiation of patients with long-wave ultraviolet light (UVA) 2 hr after oral 8-methoxypsoralen (8-MOP), has been used since 1974[5] for psoriasis and other dermatoses and is one of the most effective treatments for psoriasis vulgaris. The clearing phase of this treatment is beneficial in about 80% to 90% of patients.[2, 14–16, 20, 21] This success rate appears to be independent of the wide range of interindividual variations of 8-MOP concentrations in blood.[7, 8, 22]

Our purpose in this prospective study was to investigate intraindividual variations in comparison with interindividual variations of 8-MOP concentrations in serum and to find out whether results of the clinical test, expressed as the minimal phototoxic dose (MPD),[25] correlated with these variations. We designed a longitudinal study in which all patients took methoxsalen tablets of the same batch number to evaluate possible intraindividual changes in 8-MOP serum levels in the course of time. Interstitial fluid concentrations of 8-MOP near the epidermis, represented by concentrations in suction blister fluid (sbf),[9, 12, 13, 23] were determined to see whether there was a relationship among these concentrations, the serum levels, and the MPD.

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Reprint requests to: Prof. Dr. F. A. De Wolff, Laboratory of Toxicology, University Hospital, 2333 AA Leiden, The Netherlands.

Methods

Our subjects were 20 psoriatic patients who agreed to take PUVA therapy for the first time.

Abbreviations used

AUC: Area under the serum concentration/time curve, calculated by the trapezoidal method up to 5 hr (AUC_{0-5}) and extrapolated to infinity ($AUC_{5-\infty} = \frac{C_5}{\beta}$, where C_5 is the observed plasma concentration at the last sampling time, i.e., 5 hr).

β: Rate constant of elimination, calculated as the slope of the last linear phase of a ln serum concentration–time plot.

Cl: Intrinsic clearance, $Cl = \frac{dose}{AUC_{0-\infty}}$ (l/hr).

C_{max}: Maximal serum concentration of 8-MOP (ng/ml) after drug intake.

C_{sbf}: Concentration of 8-MOP (ng/ml) in suction blister fluid.

8-MOP: 8-Methoxypsoralen.

MPD: Minimal phototoxic dose (J/cm²).

PUVA: Psoralens with ultraviolet A.

sbf: Suction blister fluid.

t_{max}: Time of maximal serum concentration after drug intake (hr).

t½: Half-life of elimination: $t½ = \frac{\ln 2}{\beta}$ (min).

Vd: Relative volume of distribution in l/kg: $Vd = \frac{Cl}{\beta \cdot \text{body weight}}$

Patients on long-term medication, including oral contraceptives, were excluded, and those who had to start other medication during the study were dropped. Patients who developed an intercurrent disease or failed to receive PUVA treatment more than once were also dropped. All participants had to conform to the rules of the PUVA treatment.[6]

On 3 days during the first month of therapy 3 experiments were performed, i.e., on the first day, 3 days later, and 1 mo after the start (the twelfth or thirteenth treatment session). On the day before each experiment the patients were not permitted to eat after 8 P.M. but could drink water or tea without milk. On the day of the experiment, fluid intake was unlimited; however, coffee, cocoa, and milk (or milk products) were prohibited. Food was not allowed except as indicated until the tests were completed. The patients took 10-mg methoxsalen tablets (Meladinine, Basotherm GmbH; charge No. 7004) 0.5 to 0.7 mg/kg body weight, with a glass of water on an empty stomach, followed by a slice of bread spread with jam. Two hours later tests to determine the MPD were performed at a lesion-free site on one of the buttocks according to the principles of phototesting in photochemotherapy.[25] The doses were 1.5, 2, 4, 5, 7, and 9 J/cm².[2] At 30-min intervals starting just before 8-MOP intake, blood was collected for 5 hr through a butterfly cannula inserted into an arm vein. Three hours after the start, patients ate two slices of bread with jam.

Three days later the same procedure was followed except that after the second MPD test (the first having been read by then), all three test areas were covered and the first total body irradiation was applied on the basis of the results of the first MPD test. The second test was read 3 days later. From then on, irradiation was performed three times a week; and the area that was to be tested a month later was covered.

After a month the same procedure was followed except that suction blisters were drawn during the first 2 hr after 8-MOP intake. Two round Plexiglas boxes (4 cm in diameter) were used for this purpose. Each was provided with seven round holes (0.5 cm in diameter) connected with a vacuum pump providing a pressure of 200 mm Hg below atmospheric pressure.[8, 9] Just before the last MPD test the first sample of sbf was collected with a Mantoux needle attached to a 1-ml syringe. The second sample, and if possible a third and fourth, were drawn 3, 4, and 5 hr later (seven blisters yielding approximately 0.5 ml). After the third MPD test a normal PUVA treatment was given, and the test was read 3 days later.

A fourth 8-MOP serum curve was obtained for 15 of these 20 patients between 2 and 6 mo after the clearing phase while the patients were on maintenance PUVA therapy (one irradiation every 14 days). The same procedure was followed as on the other test days except that the MPD was not determined nor sbf drawn; only the usual irradiation was performed. For determination of 8-MOP in serum (1 ml) and sbf (0.2 ml) an HPLC method was developed (described elsewhere[8]).

Results

One of the 20 patients admitted to the trial decided to stop PUVA therapy, and several blood samples from another patient were lost. Before test 4 three other patients stopped PUVA therapy, one moved away (No. 8), one had to stop because of "terrible itching" (No. 13), and the third had no clearing of the psoriasis lesions during the initial treatment (No. 9).

Kinetics of 8-MOP in serum. In Table I kinetic data of the remaining 18 patients are given. The time of maximal serum concentration after drug intake (t_{max}) averages between 1.5 and 1.8 hr on the 4 test days. There is no significant difference in mean t_{max} among test days 1 to 4. Mean maximal serum concentration (C_{max}) after oral intake of 0.6 ± 0.06 mg 8-MOP/kg (mean ± SD) on the 4 test days (1 to 4) is in the range of 155 to 176 ng/ml. There are intraindividual fluctuations in C_{max}, but these are minor in comparison with the variations of C_{max} among patients. Some patients have a consistently low C_{max} on the 4 test days; others are constantly at a high level.

Mean AUC values on the 4 test days range between 420 and 551 ng · hr/ml and do not differ significantly. Intraindividually the AUC values vary, but this fluctuation is small in comparison with the variation among patients. Mean t½ values on days 1 to 4 range between 61 and 77 min and do not show a significant difference. Intraindividual and interindividual variations are relatively large.

Table II shows the intrinsic clearance (Cl) on test days 1 to 4 with individual means and the means per test day of all 18 patients. Means per test day do not differ significantly, but mean Cl values per patient vary greatly. In this table the values of the relative volume of distribution (Vd) are also presented. The correlations between the different kinetic parameters are found in Table III. There is a positive relationship among C_{max}, AUC, and Cl. Cl seems to determine the height of C_{max} and the AUC.

Kinetics of 8-MOP in sbf. Table IV shows 8-MOP concentrations in sbf on the third test day (1 mo after starting PUVA therapy) and means per individual of these levels at 2 to 5 hr. The sbf concentrations are lower than corresponding serum levels and do not fluctuate over the 3-hr period in which they were measured as much as the 8-MOP serum concentrations. Concentration of 8-MOP (ng/ml) in sbf (C_{sbf}) is 30% ± 13.7% (mean ± SD; n = 16) of C_{max}. The number of patients for the statistical calculations of the sbf data is 16. Suction failed in patient 7 because of loss of vacuum. Patient 1 had an erythrodermatous skin, which made the MPD test difficult to evaluate, and the suction blisters were on inflmed skin. Therefore high sbf–8-MOP concentrations (Table IV) are encountered in this patient with low C_{max}, low AUC, and a high Cl (Tables I and II). For this reason patient 1 was not included in the statistical analysis of sbf and MPD data. For two other patients (Nos. 2 and 5) only one sbf sample could be drawn. Table III shows that the mean of the C_{sbf} at 2 and 3 hr correlates with the serum C_{max} of the third test.

Relationship between 8-MOP kinetics and effect. Table IV shows the MPD for tests 1 to 3 during the first month of the experiment as well as the mean value for the three tests. Intraindividual MPDs were remarkably constant in most patients during the first month with some exceptions. The skin types in Table IV are classified according to Wolff[25]; no correlation could be found between skin type and C_{sbf} or MPD in this material. A correlation (Table III) is found between C_{sbf3} (2 to 3 hr) and MPD_3. Good correlations are also found between MPD_{1-3} and C_{max1-3} or Cl_{1-3}.

Discussion

No significant difference was found among test days 1 to 4 for all the mean kinetic parameters used, such as t_{max}, C_{max}, AUC, t½ and Cl. Comparison of the interindividual kinetic data presented in Tables I, II, and IV, however, shows patients with a constantly high C_{max}, AUC, and C_{sbf}, a corresponding low Cl and MPD, and vice versa. This interindividual variability is in accord with other reports.[17, 24] With the exception of patients 5 and 15, the intraindividual differences in C_{max} generally vary no more than 200%.

From the significant relationship among C_{max}, AUC, and t½ on the one hand, and Cl on the other (Table III), it may be concluded that the Cl of 8-MOP, which is a measure of the activity

Table I. *Individual kinetic data on the 8-MOP levels in serum on 4* test days during PUVA therapy*

Patient No.	t_{max} (hr)				C_{max} (ng/ml)				
	1	2	3	4	1	2	3	4	Mean
1	1.5	1.5	2.0	3.0	60	98	115	86	90
2	1.5	2.0	4.0	2.0	228	309	177	297	253
3	2.5	1.0	1.5	1.5	95	221	213	264	198
4	2.0	1.5	2.0	1.5	203	288	290	258	260
5	1.5	1.0	2.0	2.0	66	51	109	24	62
6	1.0	2.5	1.0	1.5	74	58	119	84	84
7	1.0	2.0	1.5	1.0	290	193	264	360	277
8	0.5	1.0	1.5	—	41	86	57	—	61
9	0.5	1.0	3.0	—	318	168	200	—	229
10	2.5	3.0	1.5	2.5	132	171	176	135	155
11	2.0	3.0	3.0	2.0	258	231	266	217	243
12	1.0	1.5	1.5	1.5	319	311	222	258	277
13	3.5	0.5	1.0	—	137	230	261	—	209
14	1.5	1.0	1.0	1.5	82	155	145	135	129
15	1.5	1.0	1.5	1.5	73	65	24	151	78
16	1.0	0.5	0.5	1.0	170	260	157	212	200
17	0.5	2.0	1.5	2.5	210	120	215	133	170
18	2.0	1.0	2.5	1.0	41	60	80	32	53
Mean	1.5	1.5	1.8	1.7	155	171	172	176	
SD	0.79	0.77	0.86	0.59	97	90	77	99	
n	18	18	18	15	18	18	18	15	

*Patients 8, 9, and 13 were tested on 3 days; see Results.

Table II. *Intrinsic Cl and relative Vd per patient*

Patient No.	Cl (l/hr)					Vd (l/kg)
	1	2	3	4	Mean	
1	351	170	138	193	213	3.18
2	42	44	59	79	56	1.46
3	161	83	105	98	112	2.48
4	61	37	32	44	43	1.13
5	247	305	119	421	273	5.83
6	245	239	189	180	213	5.04
7	78	60	57	42	59	0.88
8	656	317	435	—	469	8.92
9	75	97	108	—	93	1.81
10	99	79	64	81	81	1.60
11	46	39	45	63	48	1.14
12	39	43	52	58	48	1.44
13	84	27	45	—	52	1.43
14	203	122	119	136	145	2.55
15	367	404	1667	193	658	7.21
16	96	67	109	80	88	2.14
17	115	134	79	134	115	1.60
18	417	425	519	512	468	7.49
Mean	188	149	219	154		3.22
SD	167	131	385	138		2.55
n	18	18	18	15		18

of the enzymes involved in its metabolism, determines C_{max}, AUC, and t½. From its short t½ and its extensive metabolism it is suggested that 8-MOP has high first-pass elimination.[8, 18, 19] The interindividual differences in serum kinetics of 8-MOP are probably the variability in Cl, and intraindividual variation is due to variation in hepatic blood flow or rate of absorption.

In investigations by others[17–19] on the interindividual variability of 8-MOP levels, no basis for it could be found. Differences in intestinal absorption could be the cause. We eliminated, however, all known external factors influencing the uptake by using a formulation of one batch number, a standard diet, and standardized time of drug ingestion in relation to food intake.[10, 11] It is therefore unlikely that interindividual variations in 8-MOP kinetics can be explained at the gastrointestinal level. The Cl is therefore the main determining factor for the interindividual levels of C_{max}, AUC, t½, and Vd, and not the variabilities in intestinal absorption.

Since serum C_{max} correlates strongly with C_{obs} (mean = 2 to 3 hr) (Table III), C_{max} has a

$AUC_{0-\infty}$ (ng · hr/ml)					t½ (min)				
1	*2*	*3*	*4*	*Mean*	*1*	*2*	*3*	*4*	*Mean*
114	235	289	207	211	47	41	51	53	48
945	908	676	456	749	121	84	74	49	82
249	479	380	408	379	63	52	55	45	54
659	1080	1244	910	973	87	99	134	83	101
162	131	337	95	181	34	82	71	117	76
163	167	212	222	191	48	58	54	69	57
510	671	699	946	706	40	54	51	82	57
61	126	92	—	93	72	60	46	—	59
531	413	369	—	438	59	72	45	—	59
403	505	621	492	505	45	57	58	44	51
1077	1291	1107	788	1066	100	131	121	80	108
1037	922	771	690	855	64	63	67	65	65
476	1495	897	—	956	84	281	68	—	144
197	328	335	293	288	52	52	48	54	51
109	99	24	209	110	31	38	42	35	36
417	601	371	501	472	55	63	62	75	64
348	299	412	298	339	48	38	48	34	42
96	178	77	78	107	46	56	35	48	46
420	551	495	439		61	77	63	62	
326	426	347	282		24	56	26	22	
18	18	18	15		18	18	18	15	

Table III. *Correlation and probability levels of differences between means*

		n	*r*	*P two-sided*
Mean C_{max}	Mean AUC	18	+0.89	0.000001
Mean C_{max}	Mean Cl	18	−0.80	0.00001
Mean AUC	Mean Cl	18	−0.74	0.00023
Mean AUC	Mean t½	18	+0.75	0.00014
Mean Cl	Mean t½	18	−0.45	0.029
C_{max3}	C_{sbf3} (mean 2-3 hr)	16	+0.64	0.0038
C_{sbf3} (mean 2-3 hr)	MPD_3	16	−0.71	0.0011
Mean C_{max1-3}	Mean MPD_{1-3}	17	−0.82	0.00003
Mean Cl_{1-3}	Mean MPD_{1-3}	17	+0.73	0.0004

Mean = intraindividual means for four test days; C_{max3} etc. = C_{max} on third test day; and r = correlation coefficient.

predictive value for 8-MOP skin concentrations. The observations in sbf of patient 1 had to be excluded from the statistical calculations because the erythematous skin hampered accurate reading of the MPD. The inflammation of the skin also led to divergent interstitial fluid ratios with respect to plasma and lymph proteins,[1, 4] apparently resulting in a high sbf/serum ratio with respect to 8-MOP concentrations (0.7; normal value is approximately 0.3).

Earlier investigations on the concentration of 8-MOP in sbf, as a model for interstitial fluid near the epidermis[8], revealed that 8-MOP levels amount to 30% to 40% of the serum concentration. Since 8-MOP is 90% bound to serum proteins[3] and sbf contains only 30% to 40% serum proteins,[8, 9, 17] the 8-MOP concentration in sbf can be expected to be 30% to 40% of that in serum. In our study the C_{sbf}/C_{max} ratio was 0.30.

Table IV. *Concentrations of sbf determined on third day of experiments and three minimal MPD tests performed during first month of PUVA therapy*

Patient No.	Test	8-MOP (ng/ml) in sbf				Mean sbf	MPD (J/cm²)	Mean MPD	Skin type
		2 hr	3 hr	4 hr	5 hr				
1	1						>9*		
	2						>9	>9	
	3	95	67	—	—	81	>9		II
2	1						1.5		
	2						4	2.3	
	3	70	—	—	—	70	1.5		I
3	1						4		
	2						4	3.3	
	3	77	160	—	—	118	2		III
4	1						1.5		
	2						1.5	1.5	
	3	75	89	112	—	92	1.5		III
5	1						4		
	2						4	4.0	
	3	—	27	—	—	27	4		III
6	1						4		
	2						4	4.6	
	3	25	9†	9	—	14	5		III
7	1						1.5		
	2						1.5	1.6	
	3	—	—	—	—	—	2		II
8	1						7		
	2						4	6.0	
	3	16	22	27	—	22	7		III
9	1						1.5		
	2						1.5	2.6	
	3	9	28	35	—	24	5		III

*>9 = no MPD could be established.

†For statistical analysis, detectable but unquantifiable levels below 10 ng/ml were taken to be 9 ng/ml.

Table III shows that the biologic effect of PUVA therapy, expressed as the MPD, correlates with C_{max} in the same order of magnitude as with the C_{sbf} or Cl. This means that the Cl also determines the MPD and thus the response of the skin to PUVA. It is remarkable that the MPD, which is a rather subjective test, correlates so well with 8-MOP kinetics in serum and sbf.

In conclusion we found evidence that interindividual variability of 8-MOP kinetics is caused by differences in metabolic capacity for this drug. Since the biologic effect is dependent on the concentrations in sbf, which are in turn fixed by the clearance-dependent C_{max}, it also appears that the biologic response to PUVA is determined by the individual rate of 8-MOP metabolism.

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References

1. Allison JH, Bettley FR: Investigations into cantharidin blisters raised on apparently normal skin in normal and abnormal subjects. Br J Dermatol 70:331-339, 1958.
2. Burger PM, Tijssen JGP, Suurmond D: Photochemotherapy of psoriasis: Clinical study of clearing and long-term maintenance treatment. Dermatologica 163:213-228, 1981.
3. Busch U, Schmid J, Koss FW, Zipp H, Zimmer A: 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, 1978.
4. Cotran RS, Majno G: A light and electron mi-

Table IV. *Cont'd.*

Patient No.	Test	8-MOP (ng/ml) in sbf				Mean sbf	MPD (J/cm²)	Mean MPD	Skin type
		2 hr	3 hr	4 hr	5 hr				
10	1						1.5		
	2						2	1.6	
	3	49	90	—	—	69	1.5		III
11	1						1.5		
	2						4	2.5	
	3	41	37	67	—	48	2		IV
12	1						1.5		
	2						1.5	1.5	
	3	58	58	34	38	47	1.5		III
13	1						2		
	2						1.5	1.6	
	3	74	53	56	44	57	1.5		II
14	1						>9		
	2						4	7.0	
	3	21	28	30	—	26	7		III
15	1						4		
	2						>9	6.0	
	3	25	9	—	—	17	1.5		III
16	1						1.5	1.5	
	2						1.5		
	3	55	34	25	—	38	2		II
17	1						2	2.0	
	2						2		
	3	65	69	35	—	56	4		III
18	1						7	5.0	
	2						4		
	3	31	21	24	—	25			III

croscopic analysis of vascular injury. Ann NY Acad Sci 116:750-764, 1964.

5. Ehrsson H, Nilsson SO, Ehrnebo M, Wallin I, Wennersten G: Effect of food on kinetics of 8-methoxsalen. CLIN PHARMACOL THER 25: 167-171, 1979.
6. Epstein JH, Farber EM, et al: Current status of oral PUVA therapy for psoriasis. J Am Acad Dermatol 1:106-117, 1979.
6. Epstein JH, Farber EM, et al, Current status of oral PUVA therapy for psoriasis. J Am Acad Dermatol 1:106-117, 1979.
7. Herfst MJ, Koot-Gronsveld EAM, de Wolff FA: Serum levels of 8-methoxypsoralen in psoriasis patients using a new fluorodensitometric method. Arch Dermatol Res 262:1-6, 1978.
8. Herfst MJ, Edelbroek PM, de Wolff FA: Determination of 8-methoxypsoralen in suction-blister fluid and serum by liquid chromatography. Clin Chem 26:1825-1828, 1980.
9. Herfst MJ, van Rees H: Suction blister fluid as a model for interstitial fluid in rats. Arch Dermatol Res 263:325-334, 1978.
10. Herfst MJ, de Wolff FA: Influence of food on the kinetics of 8-methoxypsoralen in serum and suction blister fluid in psoriatic patients. Eur J Pharmacol 23:75-80, 1982.
11. Herfst MJ, de Wolff FA: Difference in bioavailability between two brands of 8-methoxypsoralen and its impact on the clinical response in psoriatic patients. Br J Clin Pharmacol 13:519-522, 1982.
12. Kiistala U: Proteins in suction blisters of human kind. European Society for Dermatologic Research Meeting, Noordwijkerhout, The Netherlands, 1971. (Abstract.)
13. Korting HC, Schäfer-Korting M, Rosen-Maass E, Mutschler E: Determination of 8-methoxypsoralen levels in plasma and skin suction blister fluid by a new sensitive fluorodensitometric method. Arch Dermatol Res 272:9-20, 1982.
14. Melski JW, Tanenbaum L, Parrish JA, Fitzpatrick TB, Bleich HL, et al: Oral methoxsalen photochemotherapy for the treatment of psoriasis: A cooperative clinical trial. J Invest Dermatol 68:328-335, 1977.
15. Parrish JA, Fitzpatrick TB, Tanenbaum L, Pathak MA: Photochemotherapy of psoriasis

with oral methoxsalen and long-wave ultraviolet light. N Engl J Med 291:1207-1211, 1974.
16. Roenigk HH, Farber EM et al: Photochemotherapy for psoriasis: A clinical cooperative study of PUVA-48 and PUVA-64. Arch Dermatol 115: 576-580, 1979.
17. Schäfer-Korting M, Korting HC: Intraindividual variations of 8-methoxypsoralen plasma levels. Arch Dermatol Res 272:1-7, 1982.
18. Schmid J, Prox A, Zipp H, Koss FW: The use of stable-isotopes to prove the saturable first-pass effect of methoxsalen. Biomed Mass Spectrom 7:560-564, 1980.
19. Stolk LML: Farmacokinetische en biofarmaceutische aspecten van enige in de dermatologie gebruikte psoraleenderivaten. Rodophi, Amsterdam, 1982. (Thesis.)
20. Suurmond D, Burger PM, Schothorst AA, Smit AFD, van Vloten WA, Polano MK: Ervaringen met de fotochemotherapie met 8-methoxypsoraleen per os en langgolvig ultraviolet licht (PUVA therapie) bij psoriasis. Ned Tijdschr Geneeskd 122:69-75, 1978.
21. Swanbeck G, Thyresson-Hök M, Bredberg A, Lambert B: Treatment of psoriasis with oral psoralens and long-wave ultraviolet light. Acta Derm Venereol (Stockh) 55:367-376, 1975.
22. Thune P: Plasma levels of 8-methoxypsoralen and phototoxicity studies during PUVA treatment of psoriasis with Meladinine tablets. Acta Derm Venereol (Stockh) 58:149-151, 1978.
23. Vermeer BJ, Reman FC, van Gent CM: The determination of lipids and proteins in suction blister fluid. J Invest Dermatol 73:303-305, 1979.
24. Wagner G, Hofmann C, Busch U, Schmid J, Plewig G: 8-MOP plasma levels in PUVA problem cases with psoriasis. Br J Dermatol 101: 285-292, 1979.
25. Wolff K, Gschnait T, Hönigsmann H, Konrad K, Parrish JA, Fitzpatrick TB: Phototesting and dosimetry for photochemotherapy. Br J Dermatol 96:1-10, 1977.