# 8-Methoxypsoralen Levels in Blood of Vitiligo Patients and in Skin, Ophthalmic Fluids, and Ocular Tissues of the Guinea Pig

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8-Methoxypsoralen (8-MOP) levels in the blood of vitiligo patients were determined through the use of a reverse-phase high-performance liquid chromatographic method. The overall recovery of the internal standards was 85–94%, with the lower detection limit of 8-MOP at 2 ng. Peak blood levels as low as 130 ng/ml and as high as 3892 ng/ml were obtained in patients at 1–3 h following the oral administration of 0.6 mg/kg body weight of Oxsoralen capsules (Elder Pharmaceuticals Co.). These results are consistent with the clinical observation that maximum response in phototherapy is obtained at about 2 h after oral administration of the drug. Two hours after oral administration of 0.6 mg/kg of Oxsoralen, 8-MOP levels in the epidermis, dermis, and whole skin of the guinea pig (in ng/g) were: epidermis, 330 ± 20; dermis, 89 ± 16; whole skin, 379 ± 19. Also detected were 8-MOP levels of 441 ± 22 ng/ml in aqueous humor, 166 ± 18 ng/ml in vitreous gel, 355 ± 15 ng/g in lens, and 410 ± 26 ng/g in retina. These results point to the fact that the eyes of the patient must be protected from exposure to sunlight after psoralen UV treatment, and that 8-MOP is absorbed in blood unevenly and varies from patient to patient. The fact that only 50–60% of the patients responded to psoralen photochemotherapy for vitiligo may be related to the variation of absorption of the drug in individual patients. *J Invest Dermatol 87:276–279, 1986*

Photochemotherapy, using either topical or oral 8-methoxypsoralen (8-MOP) and high-intensity long-wave UV radiation (PUVA), has become a successful modality of treatment for vitiligo [1–7]. The method is more effective for treating pigmented individuals [8,9]. Over 200 patients with vitiligo have been successfully treated at our Vitiligo Center over the past 6–7 years. When a body surface area of less than 20% is affected, 0.1% solution of Oxsoralen is applied topically, followed by irradiation with gradually increasing doses of UVA. The patients with over 20% surface involvement are treated with oral Oxsoralen capsules at a dosage of 0.6 mg/kg of body weight, followed by exposure to gradually increasing dosages of UVA. Approximately 60% of our patients respond to either topical or oral therapy [8,9]. The question that we asked was why all patients fail to respond in a uniform fashion, even when the affected areas are of similar severity and duration. We, therefore, developed a method to measure 8-MOP in blood and tissue samples using a reverse-phase high-performance liquid chromatographic (HPLC) method and measured blood 8-MOP levels on a number of patients at timed intervals.

Several authors [10–21] have reported methods for the determination of psoralens with various degrees of success. Our laboratory developed a method for the quantitative determination of 8-MOP in plasma by using thin-layer chromatographic separation of the drug extracted from blood in a solvent mixture followed by scanning fluorometric measurement on thin-layer plates [10]. For the present method we used a reverse-phase column and a solvent mixture containing water and acetonitrile in order to obtain clear-cut separation of 8-MOP and trimethylpsoralen (TMP) for the quantitative measurement of each by using an HPLC method [18].

## SUBJECTS, MATERIALS, AND METHODS

**Patients** Blood 8-MOP levels of 36 adult patients (20 males and 16 females) were determined after written informed consents were obtained. Ten-milliliter blood samples were drawn prior to oral administration of 0.6 mg/kg body weight of Oxsoralen capsules. After drug ingestion blood samples were drawn at hourly intervals up to 4 h and at 24 h. All patients involved in this study fasted overnight prior to the morning of medication and drawing of blood samples.

**Animals** Guinea pigs were used as an animal model in this study for photobiologic experiments. In addition, the guinea pig was used for measurements of 8-MOP in whole skin, epidermis, dermis, ophthalmic fluids, lens, and retina 2 h after oral administration of 8-MOP (0.6 mg/kg of body weight) in corn oil. Hair was removed from the white areas of spotted guinea pigs and the areas were marked into 2-cm squares. Each square was used for application of 0.1 ml of 0.1% 8-MOP, 0.1 ml of propylene glycol-ethanol mixture (as a blank), and 0.1 ml of the material extracted from blood of patients obtained 2 h after the drug administration. All topical applications were made in triplicate. Thirty minutes after application, the animals were exposed to a high-intensity

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Abbreviations:
HPLC: high-performance liquid chromatography(-ic)
8-MOP: 8-methoxypsoralen
TMP: trimethylpsoralen

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(UVA) source (Psoralite, Elder Pharmaceuticals Co.). The total dose applied was 1.2 J/cm$^2$. Phototoxic responses were observed at 24, 48, and 72 h.

**Materials** Crystalline 8-methoxypsoralen and trimethylpsoralen were obtained from Sigma Chemical Co., St. Louis, Missouri. Oxsoralen capsules and 1% Oxsoralen lotion were obtained from Elder Pharmaceuticals, Bryan, Ohio. Acetonitrile, HPLC grade and all other analytical-grade solvents and chemicals were obtained from Fisher Scientific Co., Silver Spring, Maryland.

**Assay** For extraction of 8-MOP from blood, fluids, and tissue homogenates, a 2.0-ml aliquot (or less for ophthalmic fluids) was mixed with 5.0 ml of 0.05 M acetate buffer, pH 3.5 in a 50-ml stoppered Pyrex tube. Sixteen milliliters of ethyl ether were added at room temperature and tubes were capped. The mixture was shaken on a reciprocating shaker for 10 min under a hood at 70–80 strokes/min. After centrifugation for 10 min at 1020 *g*, 10 ml of organic layer were transferred to a scintillation vial and the solvent was evaporated to dryness under a stream of dry nitrogen gas. Prior to HPLC analysis, the dry residue was reconstituted in 50 μl of absolute ethanol, and 10 μl were injected on the chromatographic column. For the measurements of 8-MOP levels in tissues, these were homogenized in 0.05 M acetate buffer (pH 3.5) and the drug was extracted as described above. The ophthalmic fluids were treated like blood for extraction and the measurements of 8-MOP.

**Chromatographic Parameters** The instrument used was a Varian (model 5000) high-pressure liquid chromatograph, equipped with a 254–280 nm UV detector, operated at 254 nm, with a 10-μl loop injector. The analytical column was a prepacked 30 cm × 4 mm Varian Micropack (MCH-10), containing Reverse Phase Vydac. The mobile phase consisted of a mixture of water and acetonitrile. The flow rate was 2.0 ml/min and the detector sensitivity was set at 0.16 AU, while the chart speed on the 1-mV Varian recorder (model 9176) was 1 cm/min.

**Analytical Standards and Preparation of Calibration Curves** A stock solution of 8-MOP was prepared by dissolving 100 mg of analytical grade crystalline 8-MOP in 10 ml of absolute ethanol. Suitable dilution of this standard, having 8-MOP concentration of 1 mg/ml, was also prepared in absolute ethanol. A series of further dilutions was made from the latter, so that 10 μl (injected into the column) contained 2, 5, 10, 15, and 20 ng of 8-MOP. For recovery studies, enough 8-MOP was added to 2.0 ml of blood samples so that the final concentrations in blood were 2, 5, 10, 20, and 30 ng/ml. The drug was then extracted from each sample as outlined in the assay method.

## RESULTS

The retention time for 8-MOP was 8.0 min which, with the retention time of 16.5 min for the TMP, was used as an internal standard. Table I shows the relationship between the peak heights in cm and the amounts of 8-MOP (in ng) injected onto the chromatographic column. Each point was established from an average of 7 determinations. As seen in Table I, a fairly linear relationship was obtained from external standard solutions.

**Table I.** Relationship Between the Amounts of 8-Methoxypsoralen (8-MOP) Injected onto the High-Performance Liquid Chromatographic Column and the Peak Heights

| 8-MOP Injected (ng) | Peak Height (cm) |
|---|---|
| 2.0 | 0.96 ± 0.2 |
| 5.0 | 2.64 ± 0.6 |
| 10.0 | 5.85 ± 1.2 |
| 15.0 | 8.88 ± 1.5 |
| 20.0 | 11.90 ± 2.6 |

8-MOP (2.0, 5.0, 10.0, 15.0, and 20.0 ng) was injected onto the chromatographic column and the corresponding eluted peak heights of the drug were recorded. For details, see *Subjects, Materials and Methods*. Each point is an average of 7 determinations.

**Table II.** Time Course of 8-Methoxypsoralen (8-MOP) Recovery from Blood of 20 Male Subjects (ng/ml)

| Age | 1 Hour | 2 Hours | 3 Hours | 4 Hours | 24 Hours |
|---|---|---|---|---|---|
| 32 | 516 | 870 | 480 | 226 | 0 |
| 36 | 782 | 642 | 662 | 182 | 56 |
| 28 | 85 | 101 | 130 | 95 | 35 |
| 45 | 3730 | 3892 | 490 | 107 | 0 |
| 39 | 309 | 3357 | 385 | 59 | 0 |
| 35 | 392 | 336 | 230 | 108 | 25 |
| 27 | 357 | 336 | 225 | 116 | 0 |
| 46 | 288 | 398 | 480 | 216 | 0 |
| 46 | 423 | 468 | 395 | 320 | 0 |
| 23 | 558 | 880 | 656 | 115 | 0 |
| 29 | 468 | 566 | 289 | 198 | 20 |
| 48 | 1390 | 2508 | 337 | 166 | 12 |
| 52 | 1087 | 1567 | 358 | 172 | 50 |
| 33 | 480 | 996 | 467 | 152 | 36 |
| 36 | 395 | 677 | 520 | 118 | 22 |
| 35 | 287 | 755 | 396 | 129 | 0 |
| 25 | 348 | 589 | 288 | 206 | 0 |
| 24 | 225 | 360 | 160 | 215 | 15 |
| 30 | 290 | 498 | 237 | 200 | 18 |
| 32 | 310 | 470 | 260 | 196 | 0 |

Ten milliliters of blood were drawn from each subject in heparinized tube prior to oral administration of 0.6 mg/kg Oxsoralen capsules. After the drug intake, 10 ml of blood were drawn at hourly intervals up to 4 h and then at 24 h. Extraction and analysis of 8-MOP is described in *Subjects, Materials, and Methods*. Each result was obtained by averaging duplicate assays. All predrug blood samples were negative.

The amounts of 8-MOP added to and recovered from blood varied from 83–95%. When 5.0 ng were added, per ml of blood, 4.15 ± 0.6 ng (83%) were recovered. Similarly, for 10.0 ng, 15.0 ng, and 20.0 ng 8-MOP added per ml of blood, the respective recoveries were 9.10 ± 0.5 (91%), 14.25 ± 0.9 (95%), and 17.20 ± 2.0 (86%).

Blood 8-MOP levels were determined at different times after oral administration (of 0.6 mg/kg body weight of the drug) and the results in male subjects are presented in Table II. The corresponding values for female patients are presented in Table III. As can be seen, wide variations of blood 8-MOP levels were

**Table III.** Time Course of 8-Methoxypsoralen (8-MOP) Recovery from Blood of 16 Female Subjects (ng/ml)

| Age | 1 Hour | 2 Hours | 3 Hours | 4 Hours | 24 Hours |
|---|---|---|---|---|---|
| 50 | 120 | 330 | 520 | 128 | 62 |
| 38 | 126 | 298 | 452 | 155 | 56 |
| 29 | 238 | 393 | 498 | 230 | 26 |
| 23 | 305 | 446 | 338 | 280 | 115 |
| 40 | 338 | 609 | 556 | 235 | 12 |
| 47 | 414 | 659 | 388 | 166 | 0 |
| 25 | 512 | 738 | 439 | 208 | 0 |
| 46 | 250 | 586 | 452 | 333 | 123 |
| 48 | 382 | 296 | 487 | 400 | 68 |
| 52 | 250 | 380 | 406 | 239 | 59 |
| 26 | 633 | 1217 | 830 | 236 | 36 |
| 30 | 136 | 288 | 493 | 115 | 0 |
| 35 | 322 | 659 | 652 | 219 | 0 |
| 28 | 423 | 1360 | 666 | 189 | 0 |
| 38 | 325 | 296 | 460 | 299 | 20 |
| 55 | 369 | 455 | 380 | 154 | 16 |

Ten milliliters of blood were drawn from each subject in heparinized tube prior to oral administration of 0.6 mg/kg Oxsoralen capsules. After the drug intake, 10 ml of blood were drawn at hourly intervals up to 4 h and then at 24 h. Extraction and analysis of 8-MOP is described in *Subjects, Materials, and Methods*. Each result was obtained by averaging duplicate assays. All predrug blood samples were negative.

**Table IV.** 8-Methoxypsoralen (8-MOP) Levels in Skin and Eye Tissues and in Ophthalmic Fluids of the Guinea Pig Two Hours After Oral Administration of 0.6 mg/kg of the Drug

| Tissue or Fluid | 8-MOP Recovered (ng/ml or ng/g)[a] |
|---|---|
| Whole skin | 379 ± 19 |
| Epidermis | 330 ± 20 |
| Dermis | 89 ± 16 |
| Retina | 410 ± 26 |
| Lens | 355 ± 15 |
| Aqueous humor | 441 ± 22 |
| Vitreous gel | 166 ± 18 |

[a]Results represent an average of 6 determinations. Ophthalmic tissues and fluids were pooled from 4 animals for each determination.

observed. However, the results indicate that peak blood 8-MOP levels occurred most often at 2 h after ingestion of the drug, except for a few cases. One of the 20 male patients absorbed the drug rather poorly (patient 3); 6 of the 20 male patients obtained peak 8-MOP levels of over 800 ng/ml, and 2 of the 6 patients reached peak levels of over 3000 ng/ml. In addition, 2 of the male patients obtained blood psoralen levels of 1500–2500 ng/ml. The peak blood levels of the other male patients were between 755 and 336 ng/ml. Table III shows that 7 of the 16 female patients obtained peak blood levels at 3 h, although 8-MOP levels at 2 h were sufficiently high in these patients. Two of the 16 female patients obtained peak 8-MOP blood levels of over 1000 ng/ml and 14 of 16 female patients obtained peak 8-MOP levels of 406–738 ng/ml.

Presented in Table IV are the 8-MOP levels in eye tissues, ophthalmic fluids, and skin tissues determined 2 h after oral administration (0.6 mg/kg) to the guinea pigs. Aqueous humor was drawn from the anterior chamber of the eyes with a tuberculin syringe. Vitreous gel, retina, and lens were dissected out. The extraction and determination of 8-MOP in these fluids were performed by the same assay method as for blood. The drug levels in retina, lens, aqueous humor, skin, and epidermis were higher as compared with the level in the dermis. The concentration in aqueous humor, lens, and retina was more than twice as high compared with that in vitreous gel. Similarly, the level in epidermis was more than 3 times higher than that of the dermal level of the drug.

In order to determine whether the compound, extracted from the blood and measured by HPLC, was photobiologically active, experiments were conducted using the guinea pig as the test animal. The material extracted from patients' blood was pooled, evaporated to dryness, and reconstituted in 0.5 ml of a mixture of 30% propylene glycol, 69% ethanol, and 1% acetone; 0.1 ml of the solvent, as well as the extracted material and 0.1% solutions of 8-MOP and TMP were applied in triplicate on 2-cm squares of marked skin surfaces 30 min prior to exposure to 1.0 J/cm$^2$ UVA. Phototoxic responses were noted at 24, 48, and 72 h. The results were 1+ response at 24 h; 2+ response at 48 h, and between 2+ and 3+ response at 72 h for the extracted material from blood as well as for standard 8-MOP and TMP (1+ = erythema, 2+ = erythema plus edema, and 3+ = erythema, edema, and vesiculation).

The methods used to help with the tentative identification of the compound extracted from blood were thin-layer chromatography and cochromatography with authentic 8-MOP on thin-layer plates in 2 separate solvents (900:10 benzene-ethylacetate by vol and ethylacetate:chloroform:acetone:methanol:acetic acid, 5:5:3:1:1 by vol), as well as by gas-chromatography and mass spectrometric fragmentation pattern. By gas-chromatography, the material from the blood was eluted at an identical position as authentic 8-MOP. The mass spectral fragmentation of the extracted material was also identical to that of authentic 8-MOP, producing masses at 216, 188, 173 dalton, etc., by elimination of $-CO$, $CH_3$, etc.

## DISCUSSION

By using thin-layer chromatography and scanning fluorometry we reported plasma 8-MOP level of a patient. The peak level at 2 h was 3000 ng/ml [10]. A large number of investigators, using a variety of methods, reported 8-MOP levels in psoriatric patients and normal volunteers [11–21]. The peak blood or plasma 8-MOP levels reported varied widely from as low as 2 ng/ml to as high as 3000 ng/ml [10–28]. Our results, as presented here, are generally higher than those reported elsewhere. In general, there was no clear-cut relationship between peak plasma levels, time at which the peak levels occurred, the UVA exposure time, and the therapeutic effectiveness. Ideally, patients should receive UVA treatment when epidermal 8-MOP level is highest. This time may be slightly later than the time at which peak blood level is achieved.

Murata et al [29] studied distribution of [$^3$H]TMP in the rat and found that 2 h after oral administration the drug level was of the order of 4.0 μg/ml. Also, we reported significant TMP accumulation in the whole skin and epidermis of the guinea pig [18]. We find now that accumulation of 8-MOP is also high (results in Table IV) in the whole skin and epidermis of the guinea pig after oral administration of the drug with a dose comparable to a dose in patients treated for therapeutic effectiveness.

A number of reports [30–38] indicate that photochemotherapy initiates cataract formation. Lerman and Borkman [33] demonstrated accumulation of 8-methoxypsoralen in the ocular lens of the rat. We also reported significant accumulation of TMP in ocular fluids of the guinea pig [18]. Results in Table IV show significant accumulation of 8-MOP in retina, lens, aqueous humor, and vitreous gel of the guinea pig. These results are similar to those reported by Pathak et al [3] and Stern et al [38], and point to the fact that the eyes of the patient must be protected from exposure to additional sunlight after psoralen UV treatment [34–37].

In summary, a *reverse*-phase HPLC method for measurements of 8-MOP in blood, ophthalmic fluids, retina, lens, skin, epidermis, and dermis has been developed. The lower limit of sensitivity of the method is of the order of 2 ng/ml. 8-Methoxypsoralen is preferentially localized in certain body fluids and tissues, such as aqueous humor and epidermis. Since aqueous humor, lens, and ophthalmic tissues acquire very high concentrations of psoralens for 24 h, protection of the eyes during phototherapy and prevention of exposure to the sunlight for 24 h are extremely important for prevention of blindness.

Since our results appear to be higher than those reported elsewhere, we believe that the reverse-phase HPLC method is more sensitive and would be more useful in correlating clinical responses in the photochemotherapy of skin diseases with blood levels of 8-MOP.

It also becomes necessary to determine blood psoralen levels of 40% nonresponding patients at timed intervals to determine whether the drug is absorbed sufficiently and at what time after oral administration. In case of poor blood 8-MOP levels, expected skin levels may also be very low and, hence, little or no phototoxicity or melanogenesis will occur. In such instances a better method of drug delivery at the target organ must be designed for the nonresponders.

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