

## **Interaction between 8-Methoxypsoralen and Phenytoin**

### *Consequence for PUVA Therapy*

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A patient with epilepsy and psoriasis in phenytoin therapy was treated with PUVA with no effect at all. The PUVA treatment failure was demonstrated as being due to abnormally low serum levels of 8-methoxypsoralen (8-MOP) during phenytoin therapy, while normal serum levels of 8-MOP were observed after phenytoin was discontinued. The effect is probably due to an induction of the hepatic enzyme system by phenytoin, leading to an increased metabolism of 8-MOP. Other drugs with hepatic enzyme inducing properties might possibly also interfere with psoralen metabolism with further consequences for PUVA therapy. *Key word: Psoralen.* (Received May 8, 1985).

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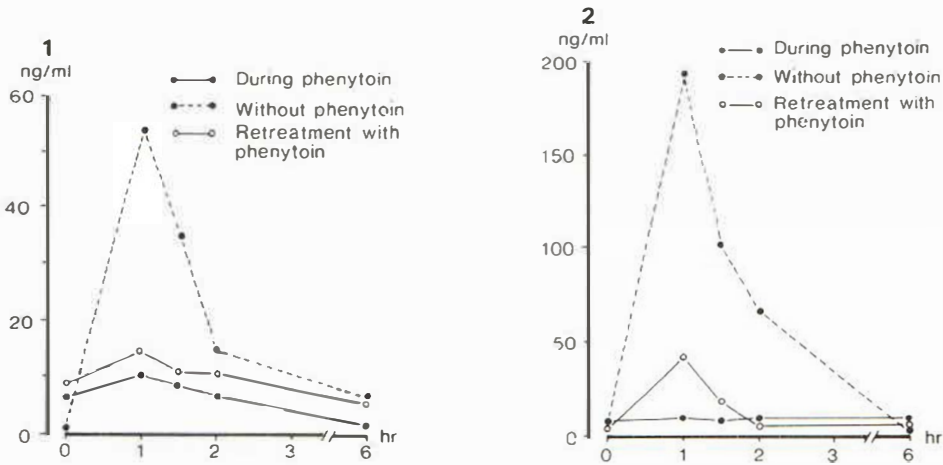


Fig. 1. Serum level of 8-methoxypsoralen after ingestion of 30 mg Meladinine.®

Fig. 2. Serum level of 8-methoxypsoralen after ingestion of 30 mg Oxsoralen.®

Several drugs are able to influence the effect of other drugs in the organism when given simultaneously. Phenytoin, barbiturates, and coumarins are examples of drugs that can alter the bioavailability of a variety of drugs (1). Drug interactions involving the furocoumarins (psoralen) used in photochemotherapy have, to our knowledge, not been described previously. In this report, we describe a patient in whom interaction between 8-methoxypsoralen and phenytoin was essential for the outcome of an initiated PUVA treatment.

## CASE REPORT

A 48-year-old woman with epilepsy had been treated with phenytoin (250 mg/day) for a period of 11 months. Because of psoriasis resistant to conventional therapy, PUVA treatment with 8-methoxypsoralen (8-MOP) (30 mg Meladinine®) was initiated. Although 12 PUVA treatments with UV-A doses up to 6 J/cm<sup>2</sup> were given, no beneficial effect and no pigmentation was observed. Due to a suspected drug interaction between phenytoin and 8-MOP, phenytoin treatment was terminated and replaced by valproate (Deprakine®, 1 000 mg daily). Concurrently, PUVA therapy was continued but had to be discontinued after 15 additional treatments due to an intense PUVA erythema with blisters.

To examine whether the primary treatment failure with PUVA was due to alterations of the bioavailability of psoralen, serum levels of 8-MOP were determined by a high pressure liquid chromatography method (2) on blood samples obtained before ingestion of the psoralen preparation, and 1 h, 1 ½ h, 2 h, and 6 h after the intake. These analyses were performed with two preparations of 8-methoxypsoralen, i.e. Meladinine® tablets (micronized 8-MOP, pHarma-medica, Denmark) and Oxsoralen® capsules (solution of 8-MOP in soft gelatine capsules, Gerot Pharmazeutica, Austria). The investigations with each product were carried out on separate days after ingestion of 30 mg 8-MOP of each preparation in the morning with a glass of milk. Lunch was not allowed until 4 hours later. These examinations were performed during phenytoin therapy, one month after phenytoin was withdrawn, and three months after starting retreatment with phenytoin.

The serum levels of 8-MOP are shown in Figs. 1 and 2. For both preparations of 8-MOP subnormal serum levels of 8-MOP were found during therapy with phenytoin, while the serum levels of psoralen were highly increased one month after phenytoin was discontinued. Three months after retreatment with phenytoin was initiated, the serum values of 8-MOP were again below normal range. During the period when these investigations were performed, the patient was also treated with Ibuprofen, Nitrazepam, Azatadin, Bendroflumethiazide and Amitriptyline. However, these drugs were given continuously without change in dose.

## COMMENT

To our knowledge, no previous reports have described the influence of other drugs on the metabolism of psoralen in the organism. The present results indicate that phenytoin has diminished the bioavailability of 8-MOP due to drug interaction. This effect might be caused by a decreased gastro-intestinal absorption of psoralen, an altered plasma protein binding, or an increased metabolism of 8-MOP due to an induction of the hepatic microsomal enzyme system caused by phenytoin.

It is well known that food intake can change the gastrointestinal absorption of 8-MOP. An increased bioavailability of psoralen was observed when 8-MOP was given together with breakfast (3), while others have demonstrated a decreased peak concentration of plasma 8-MOP, when the drug intake followed a fatty meal (4). Although phenytoin has not been demonstrated to change the intestinal absorption of other drugs, it cannot definitely be ruled out that the present results are due to an altered absorption of 8-MOP from the intestine.

The binding of psoralens to plasma proteins is relatively high, and therefore a drug-induced displacement of 8-MOP from its protein binding sites might accelerate the elimination from the body. However, in *in vitro* experiments, only tolbutamide could modify the 8-MOP protein binding to a pharmacokinetically significant extent (5).

Previously, others have demonstrated that anticonvulsants (including phenytoin) are able to accelerate the biotransformation of different drugs by inducing the metabolizing enzyme system of the liver (6, 7, 8). Similarly, our findings, that a decrease in the serum level of 8-MOP was evident during phenytoin therapy, can be explained by the same mechanism. The practical outcome of this observation is, that a treatment failure with PUVA in patients treated with phenytoin might be due to drug interaction. Furthermore, changes in phenytoin dose during PUVA therapy might lead to serious erythema or blistering reactions. In this case we have not examined whether the serum level of phenytoin was influenced by 8-MOP.

In conclusion, we have demonstrated an interaction between phenytoin and psoralen, leading to low serum levels of 8-MOP in one patient. This effect is probably due to an induction of the hepatic enzyme system by phenytoin. A great variety of drugs including ethanol and cigarette smoking are able to affect the metabolism of coumarins through a stimulation of the liver enzyme activity (1, 9). Since psoralen is a combination of furan and coumarin (furocoumarin), other drugs with hepatic enzyme inducing properties might possibly also interfere with psoralen metabolism with further consequences for PUVA therapy.

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