Chronopharmacokinetics of 5-Methoxypsoralen

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Diurnal variations in drug pharmacokinetics are a well known phenomenon. Chronopharmacology studies now appear to be attracting increasing interest with a view to establishing an optimum therapeutic prescription. In order to determine possible chronobiological variations of 5-methoxypsoralen (5-MOP) pharmacokinetic, 5-MOP blood concentrations were quantified in 8 healthy subjects after drug ingestion at different times during the day. Stolk's High Performance Liquid Chromatography technique was used to assess the 5-MOP serum concentrations. Each subject underwent three pharmacokinetic studies after oral ingestion of 5-MOP (1.2 mg/kg), in conjunction with a standardized low-lipid meal. The first pharmacokinetic study was started in the morning, the second in the afternoon and the third in the evening. Drug intake was at intervals of 2 days, to avoid drug accumulation. The results showed that the evening intake of the drug induced a higher 5-MOP maximum concentration and a higher 'area under curve' than morning or afternoon ingestion. This study suggests an optimized PUVA therapy, when performed in the evening.

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5-Methoxypsoralen (5-MOP) is a linear furocoumarin increasingly used for its skin photosensitizing effect, for the treatment of certain dermatological diseases such as psoriasis and vitiligo. 5-MOP photochemotherapy was reported to have several advantages compared with 8-MOP photochemotherapy, most notably for reducing the phototoxic response (1).

Previous studies have shown that the efficacy of PUVA therapy depends on the plasma psoralen concentrations (2,3). Moreover, it is now well known that pharmacokinetic parameters of drugs may be conditional upon the time of drug intake. The aim of this study was therefore to demonstrate diurnal variations in pharmacokinetic parameters of 5-MOP.

MATERIAL AND METHODS

Subjects
Eight healthy students (4 males, 4 females, average age 23 years) took part in this experiment. They fasted for 12 h before the administration of 5-MOP (Psoraderm-5 tablets, each containing 20 mg (Bergaderm, Rungis, France)).

Drug administration
Just before oral drug ingestion (1.2 mg/kg), a standardized low-lipid meal was given to each subject. The meal consisted of a glass of orange juice, a jam sandwich and a cup of black coffee or black tea. No additional food was allowed until the end of the pharmacokinetic study. For each participant, the morning pharmacokinetic time started at 8 a.m., the afternoon one at 2 p.m. and the evening at 7 p.m. A minimum washout interval of 2 days was kept between each pharmacokinetic study. Blood samples were collected, after 5-MOP oral administration, at 0 h, 30, 60, 90, 120, 150, 180, 240, 300 and 360 min.

The serum fractions were separated and stored at –20°C until analysed.

Assay procedure
Following extraction, 5-MOP concentrations were quantified by high performance liquid chromatography (HPLC), according to the method published by Stolk (4). This technique was chosen for its sensitivity, reproducibility and easiness.

1. Extraction of 5-MOP from serum
Reagenia (analytical quality)
- dichloromethane (DCM)
- heptane

Method
1.0 ml plasma or serum was mixed with 10 µl of the internal standard solution (8-MOP) in a glass test tube. 5 ml heptane-DCM (4:1) was added. The mixture was shaken for 5 min and centrifuged for about 7 min at 3000 rpm. Then 4 ml of the upper organic layer was transferred to a clean test tube and evaporated to dryness on a waterbath (50°C).

RESULTS
The 5-MOP pharmacokinetics for 8 subjects were evaluated for three intake times during the day. Fig. 1 shows the serum levels achieved with 5-MOP on three occasions with a single oral drug intake. Pharmacokinetic parameters are given in Table I. The mean of the 5-MOP highest concentration peaks for each intake time was 3 h after oral drug intake. These results confirm previously published data (5, 6, 7). The statistically significant highest maximal concentration (C_{max}) was obtained after the evening intake of 5-MOP (p < 0.001). No differences were observed between the morning and the afternoon C_{max}. The area under the curve, calculated for the three periods, gave significantly higher values for oral intake during the evening, as compared with the two other periods. Area under the curve (AUC) was statistically greater in the evening study than in the morning or the afternoon study (p < 0.001). The 5-MOP serum concentrations were higher when oral intake had taken place during the evening.

DISCUSSION
For most drugs, the intensity of a pharmacologic effect is proportional to the drug concentration in extracellular fluid which can enter tissues. Blister fluid resembles interstitial fluid quite closely (8). Relationships between 8-MOP serum levels and 8-MOP cutaneous blister fluid levels have been demonstrated (9). Such a relationship exists with 5-MOP (unpublished data). Moreover, in view of the relationship between serum psoralen concentration and PUVA therapy efficiency, our results suggest that PUVA therapy might be more efficient or might need a lower psoralen posology when performed in the evening. This also implies that the patient will need less UV irradiation, and then less radiation side effects.

Circadian rhythms could be one explanation for

<table>
<thead>
<tr>
<th>Sample</th>
<th>Morning</th>
<th>Afternoon</th>
<th>Evening</th>
</tr>
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<tbody>
<tr>
<td>T_{max} (min)</td>
<td>193±27</td>
<td>244±26</td>
<td>191±30</td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>82±5.9</td>
<td>89±11.05</td>
<td>175±7.45</td>
</tr>
<tr>
<td>AUC (ng min. ml^{-1})</td>
<td>1754±425</td>
<td>1757±532</td>
<td>3282±449</td>
</tr>
</tbody>
</table>

Table I. Time of maximum concentration (T_{max}), maximum concentration (C_{max}), and area under curve (AUC) (Mean ± SEM) at different oral intake times
the variation in drug bioavailability observed in our study. Indeed, circadian rhythms are prominent in the rates of drug absorption, distribution, metabolism, and excretion. Statistically significant circadian rhythms have been demonstrated for the various parameters used to characterize classical pharmacokinetics (10). Thus, the determination of pharmacokinetic parameters of 5-MOP for each patient, at different times of the day, may lead to an optimized treatment. Our study suggests that timing of drug dosing is an important therapeutic parameter that usually received too little attention.

REFERENCES

Pemphigus Vulgaris Associated with Pregnancy
A Case Report from Japan

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We present a case of pemphigus vulgaris which developed during pregnancy. The newborn infant was normal. Bullous lesions were successfully treated by pulse therapy with high-dose corticosteroids. This is, to our knowledge, the first report in English from Japan describing pemphigus vulgaris associated with pregnancy.

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Pemphigus vulgaris is an uncommon autoimmune bullous dermatosis occurring most frequently during the fifth and sixth decades of life (1). The diagnosis is confirmed histopathologically by suprabasal cleft formation and immunopathologically by IgG fluorescence in the intercellular spaces of the epidermis (2). Blistering is suppressed by adequate corticosteroid therapy.

Although pregnancy is accompanied by profound metabolic and hormonal changes, occasionally associated with a variety of skin disorders, coexistence of pregnancy and bullous dermatosis is unusual (3).