Relative Bioavailability of Oral Low Dose Methotrexate

A Comparison of 2 Different Formulations

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Summary. In 39 patients the bioavailability of methotrexate from the two tablets Emthexat 2.5 mg and Methotrexate 2.5 mg was assessed in a double-blind study after a single oral dose of 30 mg/m² Methotrexate. There was a considerable inter-individual variation of the serum pharmacokinetics in regard to \( C_{\text{max}} \) and \( t_{\text{max}} \), independent on the MTX formulation. Emthexat 2.5 mg tablets and Methotrexate 2.5 mg tablets were bioequivalent according to the definition (\( \text{AUC}_E \geq \text{AUC}_M \times 80\% \)).

Key words: methotrexate; pharmacokinetics, oral low dose formulation

A bioavailability study was undertaken with the following aims:

1) To obtain more information about the pharmacokinetics after oral administration of low dose methotrexate (MTX).

2) To compare the pharmacokinetics and the urinary excretion of MTX tablets produced by Lederle (Methotrexate) and by Pharmachemie (Emthexat).

Thirty-nine comparable patients were randomly allocated into 2 groups of a double blind study. Nineteen patients received the Methotrexate and twenty patients received the Emthexat.

After overnight fasting the patients swallowed the calculated number of 2.5 mg MTX tablets over a 20 min period together with 0.5 l fluid. After 2 h the patients had breakfast. The patients had no food restriction during the next 22 h but were encouraged to drink as much as possible during this period, at least 1.5 l. Serum blood samples for MTX concentration analysis were drawn 15 min before the MTX intake, and later on according to a fixed time schedule. Following the MTX intake the 24 h urine was collected.

The MTX concentration in serum and urine (10 ml) was determined by an enzyme inhibition assay [7], adapted to a Flexigem centrifugal analyzer (Electro-Nucleonics, Inc., Fairfield, N.J., USA).

Fig. 1. Serum concentration-time curves after oral Methotrexate (MTX) 30 mg/m² based on mean serum concentration levels. • Methotrexate (Lederle), ○ Emthexat (Pharmachemie)
Table 1. Pharmacokinetic parameters (Mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Emthexat</th>
<th>Methotrexate</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (nmol/l)</td>
<td>1142 ± 328</td>
<td>1200 ± 628</td>
<td>0.72</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>2.0 ± 0.7</td>
<td>1.6 ± 0.6</td>
<td>0.05</td>
</tr>
<tr>
<td>tl/2 (h)</td>
<td>3.3 ± 1.2</td>
<td>3.2 ± 1</td>
<td>0.78</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>3.9 ± 0.6</td>
<td>3.9 ± 0.4</td>
<td>1.00</td>
</tr>
<tr>
<td>AUC (0–12 h)(nmol/l)</td>
<td>5.20 ± 1.52</td>
<td>5.23 ± 2.22</td>
<td>0.96</td>
</tr>
<tr>
<td>MTX urine (nmol/l)</td>
<td>22990 ± 13715</td>
<td>20072 ± 10787</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Pharmacokinetics

For each patient group a serum concentration-time curve for MTX was drawn, based on the mean serum concentration values obtained in the individual patients at each time interval. Pharmacokinetic parameters were calculated from the MTX concentration-time curves in a 24-h period. Mean residence time (MRT) was derived as AUMC/AUC where AUMC was the area under the first moment concentration time curve [10]. The relative bioavailability was estimated by comparing the AUC-values for each drug preparation. The AUC for Methotrexate (Lederle) was set to 100%. Bioequivalence was defined as $\text{AUC}_E \geq \text{AUC}_M \times 80\%$

Based on the MTX concentration in the 24 h urine the amount of excreted MTX was calculated (MTX urine).

Standard statistical methods were applied (mean ± SD, two-sample t-test).

Results

The serum concentration-time curves were almost identical for the two MTX formulations (Fig. 1). A relative bioavailability of 99.4% was obtained, indicating that the two drugs were bioequivalent. There was no statistically significant difference between the mean urinary excretion of MTX in the two groups. For the different pharmacokinetic parameters there were considerable inter-patient variations (Table 1), indicated by a high standard deviation.

Discussion

This study confirms previous observations that the pharmacokinetics of oral MTX are variable and often unpredictable in the individual patient. At low doses of oral MTX (≤ 30 mg/m²) absorption from the gastrointestinal tract is believed to be almost complete [1–3, 6, 9–11]. The relative bioavailability ranges from 23 to 95% (mean 63%) [1]. At increased doses of oral MTX the absorption mechanism probably reaches a saturation point [8, 11]. As also shown in the present study “fast absorbers” can be differentiated from “slow absorbers” [11] after low dose oral MTX.

Reasons for the demonstrated pharmacokinetic variations may be inter-patient differences regarding food intake, differences of the gastrointestinal bacterial flora and/or concomitant drug medication [11]. All these factors cannot be completely controlled and standardized in the clinical situation. This relates, in particular, to the patient population in whom oral MTX may be desirable from a feasibility standpoint: The pediatric and geriatric patients [4, 5]. From a clinical point of view one should consider such inter-individual unpredictable pharmacokinetic variations as possible reasons for lacking treatment response [11].

In summary, after low dose oral MTX the clinician has to be aware of considerable inter-individual unpredictable pharmacokinetic variations both regarding the maximal serum concentration of MTX and/or the time until this concentration is reached. The two tested formulations of oral MTX (30 mg/m²) (Emthexat and Methotrexate) yield similar pharmacokinetic parameters.

Acknowledgment. This work was financially supported by the Norwegian Cancer Society.

References