WHY INTRAMUSCULAR METHOTREXATE MAY BE MORE EFFICACIOUS THAN ORAL DOSING IN PATIENTS WITH RHEUMATOID ARTHRITIS

R. A. HAMILTON and J. M. KREMER
Albany College of Pharmacy, Albany, NY 12208, USA

SUMMARY
In order to compare the relative bioavailability of orally administered methotrexate (MTX) with i.m. administration in patients with rheumatoid arthritis, we compared the pharmacokinetics of MTX at both the usual starting dose of 7.5 mg and at higher established maintenance dosages in 21 patients. Pharmacokinetic measures were repeated ~6 and 18 months after baseline while patients consumed their usual maintenance doses of MTX (17.0 ± 3.8 mg). The relative bioavailability of the usual maintenance dose of MTX was reduced by 13.5% compared with the initial dose of 7.5 mg (P = 0.026). Area under the serum concentration vs time curve (AUC) was significantly reduced with oral vs i.m. administration at usual maintenance doses (decrease of 0.729 μmol h/l by oral administration, P = 0.027), but not at a 7.5 mg dose of MTX. Clinicians using MTX should not assume constant and complete bioavailability across the dose range used to treat patients with rheumatoid arthritis. Our observations explain the reported clinical success of switching from an oral to a parenteral route of administration in patients receiving maintenance doses of MTX.

KEY WORDS: Methotrexate, Rheumatoid arthritis, Bioavailability.

METHOTREXATE (MTX) is widely recognized to be the most effective drug in current use for the treatment of rheumatoid arthritis (RA). While most patients receive 7.5 mg weekly as a starting dose, long-term prospective studies have documented the need to increase the dose of MTX in order to achieve an optimal therapeutic effect [1–5]. Indeed, the clinical efficacy of the drug is dose related [6].

While investigators have described the pharmacokinetic profile of MTX in patients with RA [7–10], no reports comparing the pharmacokinetics of the drug on the typical starting dose of 7.5 mg with the usual higher maintenance doses have yet emerged. This comparison is of potential clinical relevance as patients with RA exhibit a plateau in their clinical response to MTX after 6 months of treatment [1–5]. We had previously examined whether resistance to MTX could explain the plateau in response and were unable to demonstrate this phenomenon [11]. The present investigation addresses the question of whether altered pharmacokinetics of MTX at usual weekly maintenance doses could contribute to either the plateau in clinical response or the anecdotally reported success associated with the practice of switching from oral to i.m. MTX.

METHODS

MTX administration
As part of a long-term study of the pharmacodynamics and pharmacokinetics of MTX, 21 patients with definite or classical RA underwent pharmacokinetic studies (as described below) on multiple occasions. Initially, patients received 7.5 mg of MTX, orally and i.m. within a period of 8 weeks. The order of the route of administration was randomly assigned. Approximately 6 months after these studies, patients underwent a pharmacokinetic study following oral administration of their usual maintenance dose. This maintenance dose was determined by titration to clinical response and tolerability following initiation of therapy with 7.5 mg weekly. Approximately 18 months after the initial study, patients underwent pharmacokinetic determinations after the oral administration of another 7.5 mg dose of MTX. Approximately 30 months after the initial study, patients again underwent pharmacokinetic determinations following the i.m. administration of their usual maintenance dose. (This dose had not changed since the previous pharmacokinetic study following oral administration of the usual maintenance dose.) Patients consumed no other disease-modifying agents besides MTX throughout the study and were maintained on non-steroidal anti-inflammatory drugs (NSAIDs) which were kept constant. Twelve of 21 patients were also on low-dose prednisone during the study (Table I).

Pharmacokinetic studies
Patients received MTX, either 7.5 mg or their usual maintenance dose (as described above), orally or i.m., at 8:00 a.m. after an overnight fast. Blood samples were collected prior to the 8:00 a.m. dose and at 0.5, 1, 2, 3, 4, 6, 8, and 24 h after the dose. Urine was collected for 24 h for MTX and creatinine analysis. Blood and urine were analysed by FPIA for MTX concentration. The assay had a limit of detection of 0.01 μM and an interday coefficient of variation of 4.9%. Serum and urine creatinine concentrations were determined by the clinical laboratory. Areas under the serum concentration vs time curve (AUC) were calculated by the trapezoidal rule through 8 h. Area under the curve

© 1997 British Society for Rheumatology
from 8 to 24 h was determined using the log–trapezoidal rule or Simpson’s approximation. Area under the curve from the last measured concentration to infinity was determined by dividing the final concentration by the terminal elimination rate constant. The average area included in the terminal AUC was 6.8% of the total AUC. The terminal elimination rate constant was determined using the non-linear curve-fitting program RSTRIP. The maximum concentration ($C_{\text{max}}$) was determined as the maximum measured concentration and the time at which this was observed was the time of maximum concentration ($T_{\text{max}}$). Renal clearance was determined by dividing the urine MTX by the AUC for 24 h. Creatinine clearance was determined using standard formula.

Relative bioavailability ($F$) was determined as the ratio of the AUC for the p.o. dosing divided by the AUC for the i.m. dose. Because of the possibility of dose-dependent elimination and absorption, bioavailability determinations were made by comparing the results of comparable doses, i.e. 7.5 mg oral doses were compared with 7.5 mg i.m. doses, and the usual maintenance dose administered orally was compared with the usual maintenance dose administered i.m. Thus, $F$ was determined twice in each patient.

**Statistical analysis**

Data are summarized and presented as mean and 95% confidence intervals. Comparisons were made between the two dosing levels using two-way analysis of variance with data blocked on dose and route of administration. Statistical significance was set at the 0.05 level with a Bonferroni correction for multiple comparisons. Owing to the unusual design of this study to assess dose proportionality, stepwise linear regression was performed to determine which, if any, patient demographic or pharmacokinetic parameters were related to $F$. Specifically, the regression model was used to determine whether the duration of exposure to MTX affected bioavailability.

**RESULTS**

Patient characteristics at the beginning of the study are given in Table I. The oral and i.m. administration of a 7.5 mg dose produced similar results. The $C_{\text{max}}$ was higher following oral administration than i.m. administration (0.47 [0.42–0.52] μM oral vs 0.40 [0.35–0.45] μM i.m., $P = 0.0017$) and also occurred later ($1.54 [1.31–1.77]$ h oral vs $1.21 [0.93–1.49]$ h i.m., $P = 0.11$). The actual data for pharmacokinetic parameters are presented in Table II. The differences in pharmacokinetic parameters between doses and routes of administration are presented in Table III, along with the statistical significance of any changes.

**Maintenance doses of MTX**

Following the administration of usual (higher) maintenance doses orally and i.m., many significant differences in pharmacokinetic parameters were observed. These pharmacokinetic determinations were performed in patients receiving usual maintenance doses (mean 7.0 (3.8) mg). Following oral administration at these higher maintenance dosage levels, $C_{\text{max}}$ was lower (0.93 [0.84–1.01] μM/1 p.o. vs 1.09 [0.89–1.29] μM/1 i.m., $P = 0.11$) and occurred significantly later (1.73 [1.46–2.00] h p.o. vs 0.90 [0.68–1.12] h i.m., $P = 0.0001$). Both the AUC and the urinary recovery of MTX were lower following oral administration [(4.87 [4.20–5.54] μM·h/1 p.o. vs 5.50 [4.65–6.35] μM·h·l i.m., $P = NS$) and (9.85 [7.79–11.91] mg/24 h p.o. vs 14.24 [11.25–17.23] mg/24 h i.m., $P = 0.0001$), respectively], indicating decreased $F$ at the higher weekly maintenance doses (Tables II and III).

**TABLE I**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>7.5 mg p.o.</th>
<th>7.5 mg i.m.</th>
<th>Full dose p.o.</th>
<th>Full dose i.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>7.5</td>
<td>7.5</td>
<td>17.0 (3.8)</td>
<td>17.0 (3.8)</td>
</tr>
<tr>
<td>AUC (μmol·h/l)</td>
<td>2.631 (0.653)</td>
<td>2.617 (0.812)</td>
<td>4.872 (1.556)</td>
<td>5.500 (1.992)</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>1.055 (0.246)</td>
<td>0.919 (0.203)</td>
<td>0.547–1.485</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.654–1.704</td>
<td>0.400 (0.122)</td>
<td>0.930 (0.216)</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (μmol)</td>
<td>0.475 (0.112)</td>
<td>0.400 (0.122)</td>
<td>0.930 (0.216)</td>
<td>1.089 (0.465)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>1.535 (0.544)</td>
<td>1.210 (0.651)</td>
<td>1.733 (0.637)</td>
<td>0.897 (0.308)</td>
</tr>
<tr>
<td>Urinary MTX (mg)</td>
<td>5.578 (1.675)</td>
<td>5.426 (2.107)</td>
<td>9.85 (4.82)</td>
<td>14.24 (7.00)</td>
</tr>
<tr>
<td>Renal Cl (ml/min)</td>
<td>94.9 (36.5)</td>
<td>90.0 (44.1)</td>
<td>82.8 (38.9)</td>
<td>99.8 (38.4)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>21</td>
<td>18</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Creatinine Cl (ml/min)</td>
<td>84.0 (26.1)</td>
<td>75.8 (33.4)</td>
<td>78.4 (28.0)</td>
<td>86.7 (27.7)</td>
</tr>
</tbody>
</table>

AUC, area under the serum concentration vs time curve; $C_{\text{max}}$, maximal drug concentration after dosing; $T_{\text{max}}$, time when $C_{\text{max}}$ is achieved; urinary MTX, urinary excretion of MTX in the 24 h period following MTX administration; renal Cl, renal clearance of MTX; creatinine Cl, creatinine clearance.
Mean differences between pharmacokinetic parameters \( n = 21 \) for all comparisons except where noted, data presented as mean (S.D.)‡

<table>
<thead>
<tr>
<th>Parameter</th>
<th>7.5 i.m.–7.5 p.o.</th>
<th>fd i.m.–fd p.o.†</th>
<th>fd p.o.–7.5 p.o.†</th>
<th>fd i.m.–7.5 i.m.†</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (μmol · h/l)</td>
<td>−0.014 (0.596)</td>
<td>0.628 (1.204)</td>
<td>2.241 (1.213)*</td>
<td>2.883 (1.654)*</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>−0.075 (0.095)</td>
<td>0.159 (0.434)</td>
<td>0.455 (0.220)*</td>
<td>0.689 (0.462)*</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (h)</td>
<td>−0.326 (0.894)</td>
<td>0.836 (0.752)*</td>
<td>0.198 (0.773)</td>
<td>−0.312 (0.905)</td>
</tr>
<tr>
<td>Urinary MTX (mg)</td>
<td>0.013 (2.035)</td>
<td>4.90 (6.35)*</td>
<td>4.09 (4.80)*</td>
<td>8.31 (7.90)*</td>
</tr>
<tr>
<td>Renal Cl (ml/min)</td>
<td>3.88 (35.6)</td>
<td>20.8 (41.4)</td>
<td>−14.5 (30.7)</td>
<td>8.2 (54.4)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>18</td>
<td>19</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Creatinine Cl</td>
<td>11.0 (28.4)</td>
<td>8.6 (28.8)</td>
<td>−9.06 (27.7)</td>
<td>8.9 (26.7)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>17</td>
<td>18</td>
<td>18</td>
<td>17</td>
</tr>
</tbody>
</table>

* \( P < 0.05 \).
‡fd, full dose.
§A positive value denotes a decrease in the second parameter and a negative value denotes an increase.

AUC, area under the serum concentration vs time curve; \( C_{\text{max}} \), maximal drug concentration after dosing; \( T_{\text{max}} \), time when \( C_{\text{max}} \) is achieved; urinary MTX, urinary excretion of MTX in the 24 h period following MTX administration; renal Cl, renal clearance of MTX; creatinine Cl, creatinine clearance.

7.5 mg vs maintenance doses

Comparison of the differences in pharmacokinetic parameters between oral administration of 7.5 mg and usual oral maintenance doses is given in Table III. As expected, AUC, \( C_{\text{max}} \) and urinary recovery of MTX are significantly higher with the usual oral maintenance dose than the 7.5 mg dose. The relative bioavailability of the usual oral maintenance dose was reduced by 13.5% (95% confidence interval 3.4%, 27.5%) compared to the 7.5 mg dose (\( P = 0.026 \)). \( T_{\text{max}} \) was not significantly different between the two groups. Renal clearance decreased when patients received their usual maintenance dose as opposed to the 7.5 mg dose orally, but this reduction did not achieve statistical significance.

Comparison of i.m. administration of 7.5 mg and usual maintenance doses revealed that AUC, \( C_{\text{max}} \) and urinary recovery of MTX are significantly higher with the usual maintenance dose than the 7.5 mg dose. In addition, the \( T_{\text{max}} \) was significantly earlier for the usual maintenance dose compared to the 7.5 mg dose. Renal clearance was similar at both the 7.5 mg dose and the usual maintenance dose.

Predictors of \( F \)

The stepwise regression indicated that \( F \) was significantly related to creatinine clearance, dose and AUC. Dose was a negative predictor of \( F \), i.e. as dose increased, \( F \) decreased. The \( R^2 \) for the regression model was 0.267 and the model indicated that these predictors were statistically significant (\( P < 0.001 \)). Duration of therapy did not enter into the model as a significant predictor of \( F \).

DISCUSSION

The results of this study are consistent with general pharmacokinetic principles and with certain aspects of previous reports of MTX pharmacokinetics. Herman et al. [7] reported 70.4% bioavailability with considerable variability following the administration of MTX 10 mg/m² i.v. to 41 patients with RA. Oguey et al. [9] administered 15 mg orally and i.v. to 10 patients, and observed bioavailability of 67%, again with considerable variability. The variability in \( F \) which we observed was ~3-fold (Table II), which is less than the almost 6-fold variability (25–149%) reported by Herman et al. [7]. This variability is due in part to intrapatient variability, and also to variable potency in the tablets and injection used for all bioavailability studies. MTX tablets may contain from 90 to 110% of the labelled amount of MTX, while MTX for injection may contain from 95 to 115% of the labelled amount of MTX [12]. Our observation of 100% \( F \) with 7.5 mg and 90% bioavailability with an average dose of 17.0 mg is somewhat higher than that previously reported. Other authors have utilized i.v. MTX as the standard for 100% \( F \), while our investigation used i.m. administration; thus, we are reporting relative and not absolute bioavailability. This is unlikely to contribute to the observed differences, since MTX appears to be completely absorbed after i.m. administration [13, 15, 16]. In addition, a preliminary investigation (unpub-
lished) in a small number of subjects at our own centre indicated that i.m. MTX had a bioavailability equivalent to that of i.v. MTX.

The pattern of urinary excretion of MTX is also consistent with the observations of F based upon AUC. When 7.5 mg doses of MTX were administered orally and i.m., the urinary excretion of MTX was essentially identical (difference = 0.013 mg) and not statistically significant. However, at usual maintenance doses, the difference in urinary excretion of MTX was 4.9 mg and was statistically significant.

This is the first report comparing the pharmacokinetics of different doses of MTX in the same patients with RA. The dose-dependent nature of MTX absorption is well described with oncologic doses of the drug [13–15]. Reporting on doses considerably higher than those used for the treatment of RA, Teresi et al. [13] reported mean bioavailability of 42% with MTX doses < 40 mg/m² and 17% when MTX doses exceeded 40 mg/m². Our observation that MTX F decreases with increasing dose in the same individuals in the dose ranges commonly employed in RA is unique and of potential clinical relevance. As the dose of oral MTX is increased, proportionally less MTX will be absorbed than at lower dose levels.

A stepwise linear regression model was used to examine explanations other than dose for our observations of changes in bioavailability. The model was statistically significant, but the \( R^2 \) value of 0.267 indicates that 73% of the observed variability is not explained by the model. It is important to consider that the duration of MTX therapy had no effect on the model. This was true whether it was entered in the stepwise regression, or added after determination of the final model. This would suggest that MTX F is not significantly related to the duration of therapy and that absorption of MTX is constant with time. We and others [17, 18] have previously reported that AUC actually increases (although not statistically significantly) over a 24 month period, perhaps due to observed decreases in renal clearance [17]. We would generally expect increases in AUC to result in an increased F. Because of these data and our observation of a decrease in F in patients receiving a higher dose of MTX, we feel that a time-related decrease is quite unlikely. Nevertheless, comparison of F with time is not usually performed over a 24 month period as we have done. We cannot entirely eliminate the possibility that other, unknown factors may contribute to the decrease in F we report over this 2 yr period.

An explanation for the observed reduction in F which was not considered is an increase in metabolic clearance of MTX. The impact of this possibility could be observed in two ways. First, an increase in metabolic clearance would reduce the proportional amount of MTX recovered in the urine. To eliminate the effect of oral absorption, this is best examined following parenteral administration of the drug. Approximately 72% of the drug was recovered from the urine following 7.5 mg i.m., while 84% of the drug was recovered from the urine following i.m. administration of the usual maintenance dose. This would suggest that renal clearance accounted for a similar amount of MTX elimination under both conditions, decreasing the possible role of changes in metabolic clearance. The second possible effect of increased metabolic clearance would be an increase in first-pass metabolism by the liver. First-pass metabolism is significant when a drug has a hepatic clearance which is large relative to hepatic blood flow [19]. Since the total clearance of MTX is small relative to hepatic blood flow, it would seem unlikely that an increase in metabolic clearance would account for the observed decrease in F.

We observed a significant increase in AUC and a non-significant increase in \( C_{\text{max}} \) when full-dose (17.0 [3.8 mg]) MTX was given i.m. compared with the oral route of administration. This difference in AUC was not observed between these two routes of administration at the 7.5 mg dose. In addition, as previously discussed, F also decreases between oral doses of 7.5 mg and the usual oral maintenance dose of the drug. These observations explain the success of the empiric practice of switching from oral to parenteral MTX in a patient with a diminishing clinical response on their usual maintenance dose of MTX. The 13.5% decrease in F at usual maintenance doses of the drug would be equivalent to a full MTX tablet at weekly doses of 17.5 mg or greater. As the confidence intervals extend to 27.5%, this could represent a decreased F equivalent to two full MTX tablets weekly in selected individuals given weekly doses in this range.

It would also suggest that increasing the oral dose of the drug as tolerated would produce a clinical response similar to that obtained by administering the initial oral dose of the drug i.m.

The actual decrease in F between i.m. and oral dosing may be enough to account for a difference in clinical response in certain individuals. This may be due to the need to exceed a therapeutic threshold for depletion of (unknown) reduced folate-dependent intracellular metabolic products. Clinical response to MTX is more likely to be a threshold phenomenon based upon the observations of dose-dependent response [1–6] and the common empiric clinical observation of an absence of response to MTX as the weekly dose is titrated upwards until a particular (higher) weekly dose is achieved. Thus, we believe that even the modest decrease in F we describe between the i.m. and oral route of administration at higher maintenance doses is of potential clinical relevance in large populations of patients receiving the drug. Practitioners using MTX must not assume constant and complete bioavailability across the dose range used to treat patients with RA and this must be considered in the so-called higher dose ranges now commonly being used in clinical practice.

ACKNOWLEDGEMENT

This work was supported by a grant from the National Arthritis Foundation.
REFERENCES


