Effects of moderate renal insufficiency on pharmacokinetics of methotrexate in rheumatoid arthritis patients

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Abstract

Objectives—To determine the effects of impaired renal function on the pharmacokinetics of methotrexate (MTX) in rheumatoid arthritis (RA) patients.

Methods—77 RA patients were included in this study. MTX was administered intramuscularly (7.5 to 15 mg). Subjects were divided into four groups, according to their creatinine clearance (CL_{CR}); group 1: CL_{CR} lower than 45 ml/min; group 2: CL_{CR} between 45 and 60 ml/min; group 3: CL_{CR} between 61 and 80 ml/min and group 4: CL_{CR} higher than 80 ml/min. Blood samples were collected from each subject before drug administration and at two and eight hours after administration. Individual pharmacokinetic parameters were estimated using a Bayesian approach.

Results—MTX concentrations (total and free) were 1.3 to 1.6-times higher in group 1 than in groups 2, 3, and 4. For total and free MTX, $t_{1/2}$ eliminations were 22.7 hours in group 1, 13.5 hours in group 2, 12 hours in group 3, and 11 hours in group 4. Clearance of total MTX was 64, 92, 96, 115 ml/min in groups 1 to 4, respectively, it was 118, 163, 171, 206 ml/min in groups 1 to 4 for the free MTX, respectively. Volume of distribution averaged 2.16 l/kg in group 1, 1.92 l/kg in group 2, 1.61 l/kg in group 3, and 1.56 l/kg in group 4. Elimination half life was significantly increased and total clearance was significantly reduced with the degree of renal impairment. Linear regression revealed good correlations between clearance values of MTX and creatinine clearance.

Conclusion—Individual testing is required rather than a general decrease of the MTX dose based only on CL_{CR} .

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with chronic renal failure, or physiologically reduced renal function in elderly patients.

Several studies have been performed to determine the effects of age and renal function on the efficacy, the tolerance and the pharmacokinetics of MTX.⁷⁻⁹

The purpose of this study was to evaluate the pharmacokinetic profile of total and free MTX in a group of RA patients with moderate impaired renal function.

Methods

PATIENTS

A total of 77 patients were included in this study after providing written informed consent. They were 16 men and 61 women. The mean disease duration was 167 months. Patients were eligible for inclusion in the study if they were at least 18 years of age and had RA based on the 1987 ACR criteria.¹⁰ Subject ineligibility criteria included a history of cancer, heart failure, pulmonary disease, hepatic dysfunction (transaminase activities above twice the upper limit of normal), or a positive test for human immunodeficiency virus antibodies or hepatitis B and C viruses. Forty five patients (61.6%) were rheumatoid factor positive.

For each patient, a medical history was taken and a physical examination was performed before the start of the study. Routine laboratory tests including a complete blood cell count, erythrocyte sedimentation rate (ESR), C reactive protein concentrations (CRP), liver and renal function tests were performed on admission to the study site at day zero. Clinical parameters were number of swollen joints, and Ritchie's articular index.

Subjects were classified into one of four groups on the basis of CL_{CR} : group 1, patients with CL_{CR} lower than 45 ml/min; group 2, patients with CL_{CR} between 45 and 60 ml/min; group 3, patients with CL_{CR} between 61 and 80 ml/min; and group 4, patients with CL_{CR} higher than 80 ml/min. Table 1 gives the drugs that were being taken by the patients.

STUDY DESIGN

Subjects maintained an overnight fast. Each patient received their usual dose of MTX (7.5 to 15 mg) intramuscularly.

Blood samples (4 ml) was obtained, in EDTA coated tubes, according to the following schedule: predose, two, and eight hours after administration. Within 10 minutes of collection, each blood sample was centrifuged to separate the plasma. The plasma was removed and placed into two tubes. One sample was

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Low dose methotrexate (MTX) is one of the most frequently used slow acting symptom modifying antirheumatic drugs in patients with rheumatoid arthritis (RA) because of its favourable benefit/risk profile.¹⁻⁴ Glomerular filtration is the dominant pathway of MTX elimination. The drug undergoes additionally a bidirectional transport within the renal tubule, an active secretory process utilising the general organic acid transport mechanism, and an active reabsorption process unaffected by acidic compounds.^{5,6} Consequently the MTX pharmacokinetics can be changed in patients

Table 1 Distribution of NSAIDs, folate supplementation, and other DMARDs in the population of patients

	Patients (n)			
	Group 1 $CL_{CR} < 45$ (ml/min)	Group 2 $CL_{CR} : 45-60$ (ml/min)	Group 3 $CL_{CR} : 61-80$ (ml/min)	Group 4 $CL_{CR} > 80$ (ml/min)
Prednisone	3	5	10	11
NSAIDs				
piroxicam		1	4	
tenoxicam	1	1		2
indomethacin	1		2	
diclofenac	1	2	3	5
naproxen				3
ketoprofen		1	2	1
Folic acid	2	2	2	6
DMARDs*				
tiopronin	2	1	2	1
sulphasalazine			1	2
hydroxychloroquine		2	3	3

*Three patients received more than one concomitant DMARD.

immediately stored at -20°C ; for the other sample, free drug was separated from protein bound drug by an ultrafiltration procedure.^{11 12} The ultrafiltrate was then stored at -20°C .

MTX concentrations in plasma and ultrafiltrate samples were measured by fluorescence polarisation immunoassay (TDX system, Abbott).^{11 12}

PHARMACOKINETIC ANALYSIS

As previously described,¹² we used a Bayesian approach to compute individual pharmacokinetic parameters of total and free MTX. The following pharmacokinetic parameters were estimated: the free fraction (expressed as a mean percentage), the free and total MTX elimination half lives, and the clearance of free (CL_{fb}) and total (CL_{TOT}) MTX. The volume of distribution (Vd) was calculated by the equation: $Vd = CL_{TOT}/\lambda_2$, where λ_2 is the elimination rate constant.

EVALUATION OF SAFETY

All clinical and biologically significant events caused by MTX were recorded as side effects.

They were collected at the time of MTX kinetics.

STATISTICAL EVALUATION

Results are presented as mean (SD).

For the pharmacokinetic parameters, and biological and clinical characteristics, variance homogeneity was verified using the Bartlett's test. These parameters were compared among groups using one way analysis of variance. As free and total MTX pharmacokinetic parameters have been found not to be independent, the statistical analysis was performed only on the pharmacokinetic parameters of total MTX. A p value of less than 0.05 was taken as the threshold of significance. A simple contrast test was used to compare 2 by 2 each creatinine clearance group; in this case, the level of significance was corrected for multiple comparisons and fixed at 0.008.

Results

PATIENTS

Table 2 gives the mean demographic, clinical, and laboratory findings of the patients.

There were significant difference between groups 1 and 3 and between groups 1 and 4 for ESR ($p < 0.002$).

SAFETY AND TOLERANCE

All adverse events were mild to moderate in intensity. No difference was observed between groups (data not shown). However, the number of patients included did not allow a correct evaluation of toxicity in the different groups.

PHARMACOKINETICS

Table 2 gives the mean (SD) pharmacokinetic parameters with the statistical analysis. Total MTX concentration, two hours after drug administration, was significantly higher in group 1 than in groups 3 ($p = 0.0036$) and 4 ($p = 0.00026$). Similar differences between group 1 and groups 3 ($p = 0.0004$), and 4 ($p = 0.00006$)

Table 2 Mean (SD) demographic, clinical, and biological characteristics at baseline for patients in this study, and pharmacokinetic parameters of total and free MTX

Parameters	CL_{CR} , ml/min			
	Group 1 <45	Group 2 45-60	Group 3 61-80	Group 4 >80
Total no of patients	7 F	15 F	8 M, 17 F	8 M, 22 F
Age (y)	76.4 (6.0)	67.1 (5.8)	65.5 (8.4)	52.8 (10.9)
Weight (kg)	53.3 (8.5)	54.6 (6.5)	65.6 (11.8)	71.1 (14.9)
Duration of disease (months)	144 (99)	210 (189)	172 (107)	143 (92)
Duration of MTX treatment (months)	39.3 (40.4)	52.3 (35.7)	54.6 (20.6)	52.0 (24.7)
Number of swollen joints	5.43 (3.05)	7.87 (5.13)	4.8 (6.0)	10.4 (18.3)
Ritchie's articular index	22.4 (39.8)	10.5 (10.5)	8.1 (11.6)	8.2 (7.4)
CRP (mg/l)	19.1 (16.2)	20.7 (20.5)	17.4 (19.6)	20.5 (28.3)
ESR (mm 1st h)**	49.1 (23.5)	34.1 (21.1)	23.2 (17.7)	22.9 (17.1)
CL_{CR} (ml/min)	39.8 (4.4)	55.8 (3.7)	68.1 (5.2)	103.5 (20.3)
Extend of unbound fraction (%)	54.1 (7.5)	59.8 (7.9)	58.5 (6.05)	57.4 (7.3)
<i>Free MTX</i>				
MTX concentration ($t=2h$) ($\mu\text{M}\dagger$)	0.34 (0.088)	0.28 (0.077)	0.25 (0.059)	0.24 (0.08)
MTX concentration ($t=8h$) ($\mu\text{M}\dagger$)	0.11 (0.058)	0.074 (0.027)	0.075 (0.026)	0.064 (0.023)
$T_{1/2}$ elimination (h)	22.7 (9.1)	13.7 (3.2)	12.0 (3.3)	11.5 (3.2)
CL_{fb} (ml/min)	118.5 (35.1)	162.8 (45.3)	171.1 (34.0)	206.0 (44.5)
<i>Total MTX</i>				
MTX concentration ($t=2h$) ($\mu\text{M}\dagger$)**	0.66 (0.18)	0.51 (0.13)	0.49 (0.11)	0.45 (0.12)
MTX concentration ($t=8h$) ($\mu\text{M}\dagger$)**	0.21 (0.12)	0.13 (0.052)	0.12 (0.039)	0.11 (0.04)
$T_{1/2}$ elimination (h)***	22.7 (9.8)	13.1 (2.9)	11.9 (2.6)	10.8 (3.3)
CL_{TOT} (ml/min)***	63.7 (20.3)	92.1 (23.8)	95.7 (17.1)	115.1 (19.9)
Vd (l/kg)	2.16 (0.58)	1.92 (0.49)	1.61 (0.63)	1.56 (0.57)

$\dagger$ Normalised to a 10 mg dose; one way ANOVA. ** $p < 0.01$, *** $p < 0.001$.

Figure 1 Plot of total MTX clearance compared with creatinine clearance.

Figure 2 Plot of free MTX clearance compared with creatinine clearance.

were observed eight hours after drug administration. In group 1, $t_{1/2}$ elimination (mean 22.7 hours) was significantly longer ($p < 0.0001$) than in group 2 (mean 13.1 hours), 3 (mean 11.9 hours) and 4 (mean 10.8 hours). Except between groups 2 and 3, CL_{TOT} was significantly different between groups ($p \leq 0.001$).

CORRELATION WITH CREATININE CLEARANCE

A plot of CL_{TOT} and CL_{fu} compared with CL_{CR} (fig 1 and fig 2) showed a statistically significant correlation ($CL_{fu} = 1.06 CL_{CR} + 96.4$, $r = 0.58$, $p < 0.0001$; $CL_{TOT} = 0.56 CL_{CR} + 56.5$, $r = 0.60$, $p < 0.0001$).

Discussion

This is the first study reporting the pharmacokinetics of a low dose MTX in RA patients with renal impairment. It was conducted in a large cohort ($n = 77$) of patients allowing an accurate estimation of the pharmacokinetic parameters according to the degree of renal impairment. A Bayesian approach has been used to determine individual MTX pharmacokinetic parameters, so as to minimise the number of samples collected and optimise the decision making process as to the best therapeutic dose regimen for each patient.

Concomitant therapeutic drugs and particularly NSAIDs were given to the patients entering this study. However, it has been reported that the pharmacokinetics of MTX are not modified by concomitant administration of diclofenac, piroxicam, naproxen, and ketoprofen.^{5 6 11 13} By contrast, Tracy *et al* reported a decrease in the systemic clearance of MTX in patients treated with naproxen.¹⁴ Kremer and Hamilton reported significant decreases in renal clearance of MTX but no change in total clearance when NSAIDs are taken with higher maintenance dose of MTX but not at a 7.5 mg maintenance dose.¹⁵ Corticosteroids and hydrochloroquine do not influence the pharmacokinetics of MTX.^{5 6} Although it has been proposed to combine slow acting antirheumatoid drugs, the possible interactions of these drugs have been poorly investigated.

This study shows that the elimination half life of MTX increases with the severity of renal impairment. The decrease of the total clearance of MTX is directly related to a decrease in renal function (evaluated by CL_{CR}). By comparison with group 4, this decrease was 44.7, 20, and 17% for groups 1, 2, and 3, respectively. According to the following equation: $Dose_{IR} = Dose_N \times (\text{elimination rate constant}_{IR} / \text{elimination rate constant}_N)$, we can suggest a dose reduction of 50% in patients with $CL_{CR} < 45$ ml/min at the onset of MTX treatment.

In conclusion, individual testing is required rather than a general decrease of the MTX dose based only on CL_{CR} for two distinct reasons: (1) the interindividual variability of the pharmacokinetics of MTX is high, and (2) MTX itself can be an underappreciated cause of mild impairment of renal function.⁹

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