BRIEF REPORT

PHARMACOKINETICS OF METHOTREXATE ADMINISTERED BY INTRAMUSCULAR AND SUBCUTANEOUS INJECTIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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The serum concentrations and the pharmacokinetics of low-dose methotrexate (MTX) were compared after both intramuscular (IM) and subcutaneous (SQ) injections in 5 patients with rheumatoid arthritis. Values for the observed peak concentration, the time to the observed peak concentration, and the area under the time versus concentration curve for IM injections were not significantly different from these values for SQ injections. These results suggest that IM and SQ are interchangeable routes of administration. SQ administration may be a more convenient and less painful way of administering low-dose MTX.

Methotrexate (MTX), a folic acid antagonist, has recently been approved by the Food and Drug Administration for use in patients with severe rheumatoid arthritis that is refractory to conventional therapy. The proposed beneficial effect of MTX in treating rheumatic diseases is its ability to inhibit inflammatory synovial cell turnover, decrease exudation in the joint spaces, and impair the response to histamine and other vasoactive substances (1–4). Treatment has centered around the use of very low doses administered in weekly intervals by oral (PO), intravenous (IV), and intramuscular (IM) routes (3,5–9).

The intramuscular route is a desirable choice for parenteral drug administration because of the completeness of absorption relative to the oral route, peak concentrations that are similar to those achieved using the IV route, and slower drug absorption and prolonged exposure to the drug compared with IV-administered MTX (3,6–8). As an alternative method of administration, subcutaneous (SQ) injections may also exhibit these beneficial pharmacokinetic patterns and would have the potential advantages of patient self-administration at home and greater patient comfort than with weekly IM injections given in the physician's office. In the present study, we compared the serum concentrations and the pharmacokinetic parameters of MTX after IM and SQ administration in patients with rheumatoid arthritis.

Patients and methods. The study population consisted of 5 patients (age range 45–75 years) who had severe rheumatoid arthritis and were currently receiving MTX (Table 1). All patients were under the care of a board-certified rheumatologist and had experienced an unsatisfactory response to nonsteroidal antiinflammatory drugs and intramuscular gold therapy. The patients had no history of hepatic disease, alcoholism, active peptic ulcer disease, or renal insufficiency. Patients who required additional antiinflammatory medication were permitted to continue taking their medication while receiving MTX.

Each patient received 2 treatments, 1 week apart, given in a randomly assigned order. One treatment consisted of the patient's usual dose administered IM (lateral midthigh); the other treatment was

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Table 1. Characteristics of the 5 rheumatoid arthritis patients studied

Patient	Age/sex	Weight (kg)	Methotrexate dose (mg)*
1	45/F	61	25.0
2	65/F	80	15.0
3	75/F	90	12.5
4	53/M	75	25.0
5	56/M	66	20.0

* This dose was given on 2 occasions 1 week apart: intramuscularly (IM) followed by subcutaneously (SQ) 1 week later, or SQ followed by IM 1 week later.

the same dose administered SQ (lateral upper arm). An indwelling venous cannula was used to collect serial blood samples from each patient at 0 (baseline), 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 4.0, and 8.0 hours after the injection. Blood was allowed to clot, and the serum was separated and stored at −10°C. The serum MTX concentration was determined in duplicate by a fluorescence polarization immunoassay technique using the Abbott TDx clinical analyzer (10) (Abbott Laboratories, North Chicago, IL). This analyzer is reported to have a sensitivity of 0.01 moles/liter, and has coefficients of variation within assays and between assays of 8.09% and 9.20%, respectively, for the 0.07-moles/liter control concentration, and 3.94% and 5.15%, respectively, for the 5.0-moles/liter control concentration. Assay cross-reactivity of 7-hydroxymethotrexate is reported as 1.5% (10).

Time versus concentration data for each patient receiving each treatment were fitted to the appropriate exponential pharmacokinetic model, using the RSTRIP pharmacokinetic computer software (MicroMath, Salt Lake City, UT). Response variables examined included the observed peak concentration (Cmax), time to the observed peak concentration (Tmax), area under the time versus concentration curve (AUC), and the elimination (ke) and absorption (ka) rate constants. The AUC was calculated using the trapezoidal rule. The rate constants ke and ka were estimated by iterative least-squares methods using the RSTRIP software. Cmax and AUC values were normalized for the dose, since patients received doses titrated to individual response, and are reported as Cmax/dose and AUC/dose, respectively.

The statistical significance of the observed differences in the pharmacokinetic data after administration by the different routes was evaluated using the paired-difference *t*-test for the response variables ke, ka, Cmax/dose, and AUC/dose. The Wilcoxon matched pairs signed rank test was used for differences in Tmax because it is unlikely that time is normally distributed. P values less than 0.05 were considered significant.

Results. Pharmacokinetic data for the IM and SQ routes of MTX administration are shown in Table 2. Values for the Cmax/dose were variable. Peak concentration data from the same patient after the 2 routes of administration showed that the drug concentrations were higher after the IM dose in 2 patients, higher after the SQ dose in 1 patient, and equivalent in 2 patients. The peak concentration (Tmax) occurred sooner and the rate of absorption (ka) was faster after the SQ injection in 4 of 5 patients. Percent differences in AUC/dose measurements after SQ and IM injections were 5% for patients 3 and 4, 14% for patients 2 and 5, and 25% for patient 1. The elimination rate constant (ke) was variable, and ranged from 0.14 hours^{-1} to 0.33 hours^{-1} after the SQ doses, and 0.22 hours^{-1} to 0.34 hours^{-1} after the IM doses.

Statistical data regarding the null hypothesis (that the mean difference between treatments for each

Table 2. Pharmacokinetic data comparing intramuscular (IM) and subcutaneous (SQ) administration of methotrexate in 5 rheumatoid arthritis patients*

	Ke (hours^{-1})		Ka (hours^{-1})		Cmax/dose MTX (μmoles/liter × mg)		Tmax (hours)		AUC/dose MTX (μmoles × hours/liter × mg)	
Patient	IM	SQ	IM	SQ	IM	SQ	IM	SQ	IM	SQ
1	0.23	0.33	5.67	26.75	0.08	0.08	0.53	0.23	0.36	0.48
2	0.34	0.20	2.72	5.24	0.10	0.07	1.17	0.70	0.43	0.37
3	0.30	0.29	3.42	5.44	0.08	0.09	1.03	0.50	0.39	0.41
4	0.27	0.25	1.58	5.36	0.07	0.07	1.50	1.25	0.41	0.39
5	0.22	0.14	35.30	2.19	0.12	0.07	0.25	2.00	0.61	0.71

* Ke = elimination rate constant; Ka = absorption rate constant; Cmax = observed peak concentration; MTX = methotrexate; Tmax = time to the observed peak concentration; AUC = area under the time versus concentration curve.

Table 3. Statistical analysis of the differences in the pharmacokinetic data of the IM and SQ routes of MTX administration in 5 rheumatoid arthritis patients*

Response variable	Difference†	*P*	Power to detect 20% difference	Power to detect 30% difference
Ke	0.03 ± 0.09	0.49	<0.5‡	<0.5‡
Ka	0.74 ± 19.80	0.94	<0.5‡	<0.5‡
Cmax	−0.01 ± 0.03	0.27	0.88§	0.99§
AUC	0.03 ± 0.08	0.37	0.61‡	0.90§
Tmax	0.02	>0.05	ND	ND

* ND = not determined; see Table 2 for other definitions.
† IM − SQ. Tmax value is the median; other values are the mean ± SD.
‡ Difference between IM value and SQ value was not large enough to enable rejection of the null hypothesis.
§ Null hypothesis accepted.

parameter is 0) are shown in Table 3. Calculated *P* values exceeded the significance value of 0.05 for every response variable. To estimate the possibility of a Type II statistical error (i.e., falsely accepting the null hypothesis), an analysis of power was performed to determine the power of the tests to detect clinically important differences at the 0.05 significance level. The power to detect a ≥20% difference in Cmax was 0.88, and the power to detect a ≥30% difference in the AUC was 0.90. Using these results from the power analysis, the null hypothesis for differences in Cmax and AUC was accepted. However, there was insufficient statistical evidence to either reject or accept the null hypothesis for the other parameters (Table 3).

Discussion. Several studies have compared the pharmacokinetics of MTX by the IV, IM, and PO routes of administration (6,7,11). MTX administered by injection has been shown to produce higher serum concentrations and more complete absorption than does orally administered MTX. Specifically, intramuscularly administered MTX resulted in rapid and complete absorption and in higher serum concentrations than did oral administration, and it provided peak concentrations similar to those observed following IV administration. Balis et al (12) compared pharmacokinetic data obtained after low doses of MTX were administered subcutaneously and orally to rhesus monkeys and to children with lymphoblastic leukemia. Those authors concluded that SQ administration was a feasible way to deliver MTX because it was well tolerated, efficiently absorbed, and it overcame problems of variable absorption seen after oral dosing (12).

The results of this study suggest that the SQ route achieves serum concentration versus time curves similar to the IM route. Statistical analysis suggests that the pharmacokinetic parameters are similar for these 2 routes of administration. No statistically significant differences were observed for any response variable. However, an acceptable analysis of power value of 80% was reached for the variables Cmax and AUC, but not for the variables ke and ka. Thus, undetected differences in ke and ka may exist. Although changes in ke should not be dependent upon the administration technique, differences in ke would not be unexpected, since samples were taken 1 week apart, and intrasubject variability after drug therapy is not uncommon.

The ka values showed considerable variability. The absorption rate was more rapid after SQ injection than after IM injection in all but 1 patient, whose rate of absorption was more rapid after IM administration. It is interesting to note that this patient had very little muscle mass, which may have affected the absorption rate. Slight differences in absorption rates (ka) would be expected when changing drug administration sites. Other possible factors altering the absorption rate include changes in the injection technique and differences in the distribution of blood circulation at different times.

The metabolite 7-hydroxymethotrexate has displayed significant blood concentration during metabolism and may contribute to the clinical effect of methotrexate (5). However, the concentration of this metabolite was not determined in this study, because its formation should not influence drug absorption.

The sampling interval of 8 hours seemed appropriate because it exceeded 2 drug half-lives in every case, and the drug concentrations during the 8-hour sample period approximated the limits of detection of the assay. The least-squares approach used to calculate ke and ka utilizes information from all data points to calculate the optimal fit of the function to the data; this eliminates the need for observations over several drug half-lives.

Although patient acceptance was not assessed as part of this investigation, no patients complained of problems associated with SQ administration, and most patients reported that the SQ injection was less painful than the IM injection.

These findings suggest that MTX concentrations achieved by each method of delivery are statistically and clinically similar, and that IM and SQ injections are interchangeable routes of MTX administration. Although this study is considered preliminary because of the small sample size, our data support the

routine use of subcutaneous MTX administration, allowing flexibility in the treatment of rheumatoid arthritis.

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