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Pharmacokinetics of Methotrexate Administered via the Hepatic Artery

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Summary. *The pharmacokinetics of moderate doses of methotrexate administered via the hepatic artery were studied in ten patients with cancer metastatic to the liver. Intra-arterial methotrexate showed two-compartment characteristics with a clearance of 79 ml/min/m^2, and an apparent volume of distribution of 21.2 l/m^2 body surface area. The average half-life of the early phase was 1.9 h and the terminal half-life was 14.4 h. The data were not different from those observed in similar patients after IV administration of equivalent doses of methotrexate.*

Introduction

Methotrexate (MTX) is a commonly used antimetabolite that is active against a large number of neoplasms. Several novel approaches to the administration of MTX have been employed, including intra-arterial (IA) infusion [8]. It is believed that IA administration of antineoplastic drugs into a blood vessel leading to the target organ may yield therapeutic results superior to those obtained with other routes of administration. The pharmacokinetic picture, i.e., of plasma concentration versus time in a peripheral vein, may not, however, differ appreciably from that observed for drug administered IV [3].

In an ongoing trial of combined therapy in patients with hepatic metastases, we recently carried out a study to investigate the efficacy of IA administration of certain antineoplastic agents into the hepatic artery. Evaluation of this investigation required monitoring of the serum concentration of MTX. Four or more serial samples were obtained in ten of 31 patients. Data obtained in these ten patients were subjected to pharmacokinetic analysis and are the subject of this report.

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Materials and Methods

Patients. As part of a study evaluating IA administration of MTX (Protocol 3L81, Northern California Oncology Group), MTX plasma levels were measured at various time intervals over 48–72 h. Four or more plasma samples were obtained in ten of the subjects. Because we consider four concentration levels to be the lower limit for estimation of various pharmacokinetic parameters for such a two-compartment-model drug as MTX, a kinetic analysis was carried out only in these patients.

The patients were between the ages of 50 and 74 years and were in advanced stages of one of a variety of neoplastic diseases with demonstrated hepatic metastases. The patients were treated with moderate doses of MTX plus leucovorin factor, 5-fluorouracil, adriamycin, and hepatic radiation. None of the patients had ascites and all had serum creatinine levels of less than 2 mg/dl. Clinical data for these ten patients are given in Table 1.

Study Protocol. An intra-arterial polyethylene catheter was inserted into the hepatic artery via the femoral or axillary artery and aorta under fluoroscopy. MTX administration was started within 24 h of insertion of the arterial catheter. To prevent MTX crystalluria the urine pH was kept above 7 by infusing 1–2 liters of 5% dextrose in 0.25 normal saline containing 150 mEq sodium bicarbonate/l before the start of the MTX infusion. Bicarbonate was then continuously infused at a rate of approximately 6 mEq/h over the following 24 h. The urine pH was monitored every hour for the first 12 h, and adjustments in the bicarbonate infusion were made when necessary to maintain urine pH above 7.

A total of 240 mg MTX/m^2 was infused over 3.5 h in two consecutive infusions. A loading infusion of 150 mg/m^2 was first administered over 30 min, and then 90 mg/m^2 was administered over the next 3 h. The goal of this dosage regimen was to achieve and maintain a serum concentration of at least 10 μmol/ml during the infusion period. This concentration is thought to produce pharmacologic synergism with 5-fluorouracil [1]. Thus 5-fluorouracil administration was initiated 1 h before the end of the MTX infusion.

A 10-ml blood sample was obtained from an antecubital vein at the end of the infusion and again at 6, 24, and 48 h after the infusion. One to five additional samples were obtained for eight of the subjects at various times up to 72 h after the infusion. The

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Table 1. Patient characteristics

Patient	Age	Sex	Site of adenocarcinoma	KPS[a] (%)	BSA[b] (m^2)	Previous treatment	Serum bilirubin (mg/dl)
1	56	M	Colon	100	1.85	Colectomy	0.7
2	74	M	Gallbladder	70	1.65	Cholecystectomy	15.9
3	57	M	Unknown primary	80	1.65	FU, MeCCNU	0.6
4	59	M	Colon	90	1.7	Colectomy, FU	2.4
5	67	M	Colon	70	1.96	Colectomy, XRT, FU	1.1
6	53	M	Colon	70	2.0	Colectomy, XRT, FU, L-PAM	2.0
7	59	M	Colon	80	1.84	Colectomy, FU, MTX	0.9
8	62	M	Colon	90	1.89	Colectomy, MeCCNU	0.7
9	50	F	Colon	100	1.44	Colectomy	0.9
10	53	M	Colon	80	1.85	Colectomy	4.5

[a] Karnofsky performance status
[b] BSA, body surface area

blood was collected in non-heparinized tubes, centrifuged as soon as possible, refrigerated, and protected from light until assayed.

The samples were assayed by the Clinical Pharmacokinetics Laboratory at the University of California San Francisco within 24 h of blood sampling, according to the method of Myers [9].

Data Analysis. The plasma concentration-versus-time data from the individual patients were fitted to a two-compartment model [4] with two consecutive infusion, the program DRUGFUN [5], available through the PROPHET computer system, being used [2]. The data were weighted with $1/Cp^2$ as a weighting function in the fitting procedure.

Results and Discussion

The plasma concentration-time data from a representative patient are given in Fig. 1. Computer-calculated values of the various pharmacokinetic parameters and their asymptotic coefficients of variation for the individual patients are given in Table 2.

Some of the individual values should be interpreted with caution, particularly where the coefficient of variation was high; in two of these cases, for example, the estimated terminal half-life was more than 100 h (patients 3 and 4). The fact that blood samples were not obtained beyond 48 h in these two patients would result in serious uncertainty in the values, which is reflected in the high coefficient of variation for these patients.

Furthermore, we would like to point out that the exceptionally low coefficient of variation for some of the values is the result of the low number of data points obtained and should therefore also be interpreted somewhat cautiously.

The pharmacokinetic picture obtained for these ten patients is quite similar to that seen in 15 comparable patients in our institution, who received

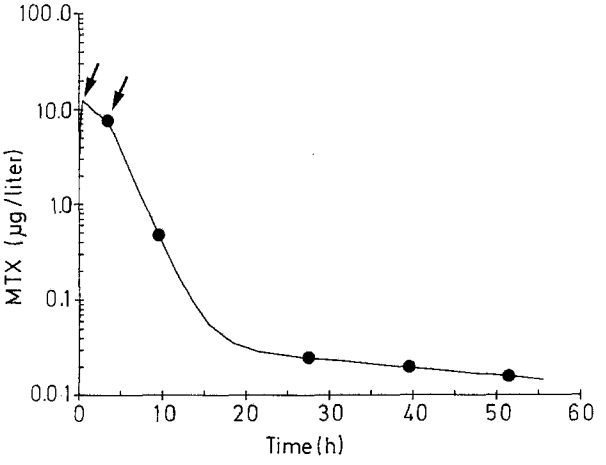

Fig. 1. Plasma concentrations of methotrexate in patient 6 (●) after an infusion of 150 mg methotrexate over 30 min and 90 mg methotrexate over 180 min. The *solid line* represents the computer-fitted concentration. The *arrows* indicate the end of the fast and slow infusion rates of methotrexate; (———) fitted; (●) observed

identical MTX therapy via IV infusion. The clearance after IA infusion in this study was 79 ± 20 ml/min versus 51 ± 20 ml/min in the patients given IV infusion. The difference was not statistically significant ($P > 0.05$). The fast elimination rate constant was also similar: $0.360 \pm 0.124\ h^{-1}$ and $0.320 \pm 0.096\ h^{-1}$ with IA and IV infusion, respectively ($P > 0.30$). The apparent volume of distribution was statistically significantly larger after IA infusion (16.1 l/m^2) than after IV infusion (10.1 l/m^2) ($P < 0.05$). The terminal (slow) rate constant was $0.043 \pm 0.027\ h^{-1}$ and the apparent steady-state volume of distribution was $15.7 \pm 8.6\ l/m^2$ during the IV infusion, values similar to those obtained in this

Table 2. Pharmacokinetic parameters of methotrexate

Patient	No. of data points	α		β		k_{21}		V_1		V_{ss}	Cl D/AUC	Cl $V_1 \cdot \alpha$
		h^{-1}	CV[a] (%)	h^{-1}	CV[a] (%)	h^{-1}	CV[a] (%)	$1/m^2$	CV[a] (%)	$1/m^2$	ml/min/m^2	ml/min/m^2
1	4	0.417	0	0.0281	0	0.0288	0	15.3	0	17.1	106	107
2	5	0.400	16	0.0629	22	0.0658	19	13.0	28	16.8	82	87
3	5	0.184	12	0.0037	1200	0.0040	1300	29.8	28	110.6	85	91
4	9	0.146	9	0.0059	600	0.0074	900	22.0	6	106.9	43	54
5	5	0.481	5	0.0511	7	0.0571	5	12.7	8	23.0	91	102
6	5	0.472	0.1	0.0184	0.5	0.0192	0.5	25.2	1.5	43.7	191	198
7	5	0.452	19	0.0207	330	0.0211	340	10.0	50	12.7	74	75
8	5	0.231	17	0.0617	6	0.0872	14	24.2	20	36.1	66	93
9	4	0.417	0	0.0796	0	0.0942	0	3.3	0	47	20	22
10	5	0.395	7	0.0357	8	0.0366	8	5.4	24	7.0	35	36
Mean	5	0.360		0.0482[c]		0.0556[c]		16.1		21.2[c]	79	87
SD[b]	5	0.124		0.0218		0.0289		8.9		14.4	48	48

[a] Coefficient of variation
[b] Standard deviation
[c] The values for subjects 3, 4, and 7 have been omitted because of the large uncertainties in the estimated values
α, β, Constants obtained graphically from biexponential decline in plasma concentrations [4]
k_{21}, Distribution rate constant from tissue to central compartment [4]
V_1, Apparent volume of the central compartment [4]
V_{ss}, Volume of distribution at steady state [4]

study (Table 2). The parameters, on the other hand, are somewhat different from those reported in other studies with IV infusion of MTX: for example, the clearance values obtained in this study are slightly larger than those observed by Stoller [10] and Isacoff [7] and smaller than that reported by Huffman [6] for IV administered MTX. Stoller and Isacoff administered 10–100 times the dose we gave and Huffman gave one-eighth of the dose we gave. As MTX kinetics have been reported to be dose-dependent [7], we believe that our intermediate clearance values are a result of the intermediate MTX doses administered. The α and β values we observed are similar to those found by Stoller [10] and Isacoff [7] after large doses of MTX, but smaller than those reported by Huffman [6]. As the rate constants are a function of both clearance and apparent volume of distribution, this could indicate not only that the clearance of MTX is dose-dependent, but also that the apparent volume of distribution is dose-dependent, with the volume becoming smaller as the dose increases.

That IA administered intermediate doses of MTX resulted in plasma concentration-time data that are similar to data from equivalent doses of IV administered MTX is not surprising. The major difference between IV and IA administration pharmacokinetically is the loss of drug to the target organ in the first pass. In light of the low hepatic clearance of MTX, only a small fraction of MTX will be lost in its passage through the liver before it can be distributed to the remainder of the body and be measured pharmacokinetically.

This lack of pharmacokinetic difference between IA and IV administration of MTX should not necessarily be interpreted as indicating a similar lack of pharmacodynamic difference. IA administration results in the delivery of higher local concentrations of drug to the target site than does IV administration, after which drug is diluted before it reaches the target organ. Such local differences, not measured by traditional pharmacokinetic analysis, may be of therapeutic benefit. Although the terminal half-life of MTX is approximately eight times longer than the fast half-life (2.3 ± 1.2 h, $n = 10$ vs 18.0 ± 10.3 h, $n = 7$), the terminal phase appears to be of little importance in calculation of the fundamental pharmacokinetic parameters, clearance and apparent volume of distribution. In Table 2 the values for clearance are listed (a) based upon the total area under the plasma concentration-time curve and (b) as the product of $\alpha \times V_1$ (rapid disposition rate constant multiplied by the initial apparent volume of distribution). It should be noted that with the exception of patient 8, the clearances derived by these two methods differed only slightly for any particular patient. Also, the difference in the mean clearance values (79 ml/min/m^2 vs 87 ml/min/m^2) was small. This suggests that steady-state plasma concentration peak and trough levels can be adequately determined from information about the α-phase alone. This

interpretation does not, however, preclude a continued *pharmacologic* response in the terminal phase, although it is *pharmacokinetically* insignificant.

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