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Enhancement of Methotrexate Absorption by Subdivision of Dose

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Summary. *A comparison was made in fasting patients between a single 100 mg oral dose of methotrexate formulated as its sodium salt in a palatable syrup and the same total quantity of drug administered in four divided doses of 25 mg taken at 2-h intervals. Allocation to the order of these treatment schedules was on a random basis. The area under the serum methotrexate concentration-time curve until 50 h was found to be considerably greater after the divided dose regimen, the mean ratio AUC 25 mg × 4/AUC 100 mg being 1.86 (± 0.90). There was no significant difference in peak serum methotrexate concentrations or methotrexate half-life estimates between the two regimens, however.*

The results of this study are consistent with saturation of an intestinal transport process when methotrexate is administered orally in a single large dose.

Introduction

The efficacy of methotrexate (MTX) as a chemotherapeutic agent has been improved by the use of high doses of the drug combined with citrovorum factor rescue [8]. Such therapy is generally given by IV infusion, but it might be of considerable practical benefit to be able to administer high doses of MTX orally. Although low doses of MTX (5–10 mg) are known to be almost completely absorbed from the gastrointestinal tract, higher doses are less well absorbed [1]. This suggests that saturation of a specialised intestinal transport process might take place. A similar state of affairs is observed with other substances such as riboflavine [5].

Methotrexate is a highly polar molecule (log P octanol = −1.85) [3], and is unlikely to be absorbed from the intestine by passive diffusion. A close structural similarity of MTX to folic acid points to the strong likelihood that the folate active transport pathway is responsible for absorption of the drug. By administering MTX in divided doses in a formulation designed to delay gastric emptying, thereby retarding transit of the drug to the site of intestinal absorption, it should be possible to avoid saturation of the uptake process. This can be conveniently achieved by formulating MTX as its sodium salt in syrup, since sugar solutions are known to retard the rate of gastric emptying [10]. The effects of divided doses of such a formulation in comparison with those of single doses amounting to the same total quantity of MTX are reported here.

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Patients and Methods

Eight patients with various forms of malignant disease (Table 1), for whom MTX therapy was considered appropriate, consented to participate in this study, which was approved by the local hospital Ethical Committee.

Methotrexate syrup was prepared from a solution of the sodium salt of MTX syrup B. P., sodium bicarbonate, and chloroform-water. The concentration of MTX was equivalent to 2 mg · ml^{-1}.

Each patient received 100 mg MTX, either as a single dose or in the form of four divided doses of 25 mg each taken at 2-h intervals. The drug was always administered on an empty stomach. After a minimum period of 1 week, each patient then received the alternative treatment regimen. Allocation to initial dose schedules (i.e., single or divided dosage) was on a random basis. After the initiation of therapy serum samples were taken at frequent intervals during the first 10 h then 12-h until 50 h had passed.

Drug levels were determined by a specific, sensitive radioimmunoassay [7] with an intra-assay precision of 4%–6% and a sensitivity of 500 pMol · l^{-1}.

The area under the individual MTX serum concentration-time curve (AUC) was computed according to the trapezoidal rule. The biological half-life ($t_{1/2}$) of MTX was derived from the slope of the regression line (log/linear least squares fitting) through the terminal portion of each serum concentration-time curve. Maximum MTX levels were read from the appropriate graphs.

Differences in MTX pharmacokinetic parameters between dosage regimens were tested for significance by means of the Wilcoxon matched-pairs signed-ranks test. To minimise interpatient variation

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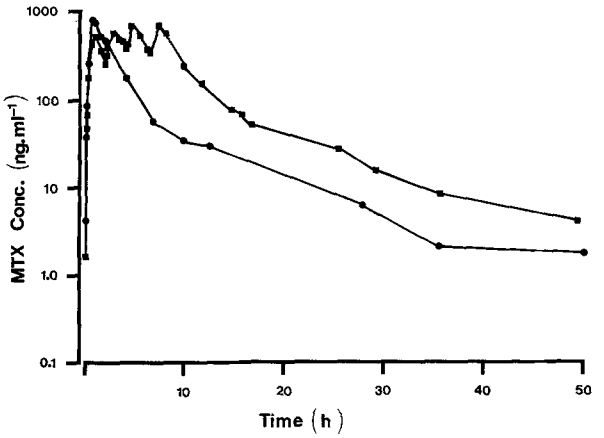

Fig. 1. Time-concentration curves for an individual given either 100 mg methotrexate in a single dose or 100 mg methotrexate divided into 4 × 25 mg, PO. ■——■, 25 mg × 4; ●——● 100 mg

the kinetic parameters ($t_{1/2}$, maximum MTX level, and AUC) obtained in each individual were compared according to the treatment regimen. The resulting ratios (25 mg × 4 ÷ 100 mg) were compared by means of the Spearman rank correlation coefficient.

Quoted errors refer to standard deviation.

Results

Typical serum concentration-time curves generated following the administration of 100 mg and 25 mg × 4 to a single patient are shown in Fig. 1. In this example, AUC following 25 mg × 4 is considerably greater than AUC after 100 mg, and this was true of the majority of the patient group. Thus the mean AUC after 25 mg × 4 was 7,499 (± 1,724) ng · h · ml^{-1}, compared with 4,990 (± 2,469) ng · h · ml^{-1} after 100 mg, this difference being significant at the 2.5% level (Table 1).

The maximum serum MTX concentrations attained were similar after both dose forms, mean values being 880 (± 283) mg · ml^{-1} after 100 mg and 841 (± 188) ng · ml^{-1} after 25 mg × 4. Similarly, individual MTX serum $t_{1/2}$ values did not differ significantly between treatment regimens. After 100 mg, the mean $t_{1/2}$ was 8.0 (± 4.7) h, compared with 7.0 (± 5.2) h after 25 mg × 4. As indicated by the standard deviations, there was marked interindividual variation in the MTX $t_{1/2}$ values.

As we have stressed, AUC after 25 mg × 4 was considerably (and significantly) greater than AUC after 100 mg in this group of eight patients. Scrutiny of the individual results, however, shows that in three patients (3, 4, and 7) the ratios AUC after 25 mg × 4/AUC after 100 mg were near unity (Table 1). In these three individuals, peak MTX levels following 100 mg were higher than the maximum concentration attained after 25 mg × 4, and MTX $t_{1/2}$ values tended to follow this pat-

Table 1. Patient details and summary of methotrexate pharmacokinetics

Patient	Clinical details	Order of study	Area under serum concentration-time curve (ng · h · ml^{-1})		Peak levels (ng · ml^{-1})		Half life (h)		Ratio of $\frac{25\times4 \text{ mg AUC}}{100 \text{ mg AUC}}$
			100 mg	25 mg × 4	100 mg	25 mg × 4	100 mg	25 mg × 4	
1	Breast carcinoma Stage II	25 mg × 4/100 mg	2,657	7,406	487	1,104	6.49	5.61	2.79
2	Carcinoma of bronchus	25 mg × 4/100 mg	1,350	4,739	608	640	1.98	4.52	3.51
3	Carcinoma of bronchus	25 mg × 4/100 mg	8,829	10,449	1,235	811	11.03	6.96	1.18
4	Breast carcinoma skin/skull secondaries	100 mg/25 mg × 4	6,436	5,995	929	657	16.22	12.73	0.96
5	Carcinoma of bronchus	100 mg/25 mg × 4	4,890	8,883	787	793	11.21	10.17	1.82
6	Anaplastic lung carcinoma	100 mg/25 mg × 4	3,522	7,054	783	690	8.61	7.90	2.00
7	Breast carcinoma Stage II	100 mg/25 mg × 4	7,225	7,732	1,309	1,160	4.47	2.97	1.07
8	Penile carcinoma – inguinal node involvement	100 mg/25 mg × 4	5,014	7,737	903	961	3.87	4.87	1.54
	Mean ± SD		4,990 ± 2,469	7,499 ± 1,724	880 ± 283	841 ± 188	7.99 ± 4.71	6.97 ± 5.22	1.86
			$P < 0.025$		NS		NS		

tern (being longer in association with higher MTX peak levels).

Consideration of the results in all eight patients together revealed a significant correlation ($r_s = 0.76$, $B < 0.05$) between 25 mg × 4 AUC/100 mg AUC ratios and 25 mg × 4 $t_{1/2}$/100 mg $t_{1/2}$ ratios. No correlation was apparent, however, between corresponding peak level ratios and AUC ratios or between peak level and $t_{1/2}$ ratios.

Discussion

This study demonstrates that the area under the serum MTX concentration-time curve is generally greater when the dose of the drug is divided. A likely explanation is that dividing an oral dose may overcome saturable intestinal absorption.

Renal clearance, which is the major process of MTX elimination from the body, is by active secretion [6], and it appears not to be altered by high doses of drug [2]. Furthermore, the data presented here reveal no consistent difference in MTX $t_{1/2}$ values for the two dosage regimens, so that MTX elimination is unlikely to have been a major contributory factor to the effect of dividing doses.

As in all comparative bioavailability studies, conclusions based on the areas under the curve depend on the consistency of half-life determination. In this small group of patients good agreement between half-lives after both regimens was obtained in all but two subjects.

The results reported here have immediate relevance to clinical practice. The toxicity of MTX is known to be dependent on the persistence of drug concentrations above a certain minimum level for a critical time period [4], and this may also be true of response to MTX therapy [9]. Increasing AUC after oral MTX would thus contribute to the enhancement of MTX effects overall (efficacy and toxicity), so that an improved response to chemotherapy might result if toxicity were satisfactorily controlled by use of citrovorum factor. Dividing the doses may therefore permit oral administration to be considered as a reasonable alternative to IV therapy.

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