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The bioavailability of oral intermediate-dose methotrexate

Effect of dose subdivision, formulation, and timing in the chemotherapy cycle

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Summary. *The oral bioavailability of methotrexate is variable and may be dose-dependent. The absorption of 'interval' oral methotrexate, which is given between cycles of chemotherapy, is unknown.*

The bioavailability of oral methotrexate has been studied in eight patients, acting as their own controls, to assess the effect of subdivision of the dose, the formulation, and the timing of the methotrexate within the chemotherapy cycle.

The mean bioavailability for all the oral methods of administration was 28.2% ± 3.7% compared with the same dose given IV. Absorption was uninfluenced by subdivision of the dose, liquid or tablet formulation, or administration on day 1 or day 10 of the chemotherapy cycle.

Introduction

Methotrexate (MTX) has been widely used as a cytotoxic agent in both haematological and solid tumours for many years [3]. Recently, in some of the more rapidly growing tumours, particularly lymphomas, MTX has been administered between the main cycles of chemotherapy to prevent regrowth of the tumour [1, 17]. This therapy (so-called interval MTX) is given at the nadir of the blood count (approximately day 10 of a 21-day cycle). The use of moderate to high-dose MTX followed by folinic acid rescue has made it possible to treat patients at this time even in the presence of depressed bone marrow function [7]. These studies have been based on IV administration of MTX [1, 17] but the oral route would be much more convenient for the patient and reduce the number of hospital visits.

The oral bioavailability of MTX is variable and may be dose-dependent. Early studies demonstrated almost complete absorption following oral administration at doses of less than 30 mg/m^2 [5, 6, 9, 10, 14, 21, 22], but erratic and incomplete absorption at doses greater than 80 mg/m^2 [5, 9, 10, 14, 18, 21]. Many of these studies were performed in small numbers of patients [10, 21, 22] and between-patient variations were often large [18–20]. Even at low doses bioavailability may be less than 20% in a significant proportion of patients [16]. The increasing use of larger doses of MTX [3] has led to a reappraisal of the absorption of intermediate doses (80–1,000 mg/m^2) [2, 4, 18–20]. Bioavailability of these quantities of MTX given as single oral doses has been shown to be approximately 20% [18, 20], but with wide variations (15%–54%) [20]. However, several workers have suggested that subdivision of the total dose into small doses given every 1–2 h may improve the bioavailability markedly [2, 4, 19].

Although oral administration would be more convenient for patients receiving interval MTX and the bioavailability might be improved by subdividing the dose, it was considered possible that absorption of MTX might be poor at a time when the previous chemotherapy (given 10 days earlier) was, perhaps, exerting its maximal toxicity on the intestinal mucosa.

The oral bioavailability of MTX given in different doses and formulations during the treatment of small cell carcinoma has been studied and compared with the bioavailability when given at the start of a cycle of therapy.

Materials and methods

Patients. Eight patients undergoing primary chemotherapy for small cell carcinoma were studied. Seven of these patients had limited small cell carcinoma of the lung (confined to one hemithorax) and one patient (patient 8) had localised but inoperable small cell carcinoma thought to arise from the oesophagus. Swallowing was not impaired and oesophagoscopy and barium swallow showed neither anatomical nor physiological obstruction. All patients were ambulant, with a Karnovsky score [12] of at least 60%, and all had normal bone marrow, renal, and liver function.

Treatment. Six patients were studied on five occasions during consecutive courses of chemotherapy, and two patients were studied on three consecutive occasions. Each patient acted as his own control. Patients received identical chemotherapy consisting of etoposide 400 mg, adriamycin 35 mg/m^2, and vincristine 1.4 mg/m^2 (maximum dose 2 mg), all IV on day 1, together with methotrexate 200 mg/m^2 given according to one of the following schedules, each giving the same total dose:

Schedule A: 4-h IV infusion
Schedule B: oral tablets 50 mg/m^2 hourly for four doses
Schedule C: oral tablets 25 mg/m^2 every 30 min for eight doses
Schedule D: oral liquid solution 25 mg/m^2 every 30 min for eight doses
Schedule E: oral tablets 25 mg/m^2 every 30 min for eight doses

Schedules A, B, C, and D were given on day 10 of the

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treatment cycle and schedule E on day 1. Folinic acid 15 mg every 6 h for 12 doses was given PO starting 24 h after the MTX.

The six patients studied on five consecutive occasions received all schedules shown above, while those treated on only three occasions received schedules A, C, and E. The order of treatments was randomised. In schedule E the MTX was given on day 1 of the first course of cytotoxic therapy (i.e., before any chemotherapy) in four patients and on day 1 of a subsequent course in four patients. Patients were fasted overnight and for 4.5 h after administration of MTX. Antiemetic therapy was not required.

Formulation. MTX tablets 10 mg were supplied by Nordic Pharmaceuticals. Oral MTX syrup was formulated from MTX injection as follows:

Sodium Bicarbonate 20 g
Methotrexate injection 80 ml (25 mg/ml)
Syrup BP 250 ml
Chloroform water BP to 1 l

The final concentration of MTX was 10 mg/5 ml. MTX injection was manufactured by Lederle Laboratories.

Sampling and assay. After an overnight fast a heparinised polythene catheter was introduced into a suitable forearm vein under local anaesthesia. A pretreatment blood sample was taken. Following the start of MTX administration either PO or IV (via a separate cannula in the other arm) blood samples were taken at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 h. Food and drink were permitted 4.5 h after the start of the study (i.e., at least 1 h after the last dose of oral MTX). Blood samples were taken into lithium heparin tubes, centrifuged, separated, and stored at −20° C until assay. Assay was performed using a commercially available enzyme immunoassay (EMIT-Syva Diagnostics). This assay cross-reacts with aminopterin but not with folinic acid. Although there is some cross-reaction with 7-hydroxymethotrexate and 2,4-diamino-N^{10} methylpteroic acid (DAMPA), this is not thought to be a problem under physiological conditions [8]. The level of sensitivity was 0.5 μg/ml and the coefficient of variation < 10%.

Statistics

The pharmacokinetic analysis was achieved using an interactive computer program, STRIPE [11]. Analysis of variance was used for the statistical analysis.

Results

The peak plasma concentrations and the areas under the curve (AUC) were similar for all four oral schedules and were not influenced by the degree of subdivision of the dose, the formulation, or the timing of the MTX dose (day 1 or day 10) in the treatment cycle (Tables 1 and 2). Mean plasma MTX concentrations for the different treatment schedules are shown in Fig. 1. In Fig. 2 the 95% confidence limits (CL) are shown for two of these schedules (IV infusion and oral tablets 25 mg/m^2 every 30 min for eight doses). The mean bioavailability of all the oral methods of administration was 28.2% (range 13.8–43.5%).

Table 1. Peak methotrexate plasma levels

Patient	Peak levels (μg/ml) schedule				
	A	B	C	D	E
1	20.9	1.6	3.5	3.7	3.8
2	20.9	4.1	3.4	3.8	5.4
3	27.7	4.2	4.0	4.1	3.3
4	17.6	2.5	2.5	3.5	2.2
5	14.8	4.6	3.8	3.3	4.6
6	4.4	0.4	1.2	0.9	0.8
7	18.0	–	3.2	–	2.2
8	9.5	–	2.0	–	1.7
Mean	16.7	2.9	2.9	3.2	3.0
95% CL	±6.0	± 2.2	± 0.8	± 1.2	± 1.3

Schedule A vs B/C/D/E: significant ($P < 0.001$)
Schedule B vs C vs D vs E: Not significant

Table 2. Methotrexate pharmacokinetics: Area under the curve and mean bioavailability

Patient	AUC μg/ml · h schedule				
	A	B	C	D	E
1	118.1	17.8	33.2	28.5	36.0
2	111.6	30.3	26.8	22.1	35.8
3	158.8	31.1	35.4	36.6	36.2
4	112.4	21.9	22.9	33.4	23.4
5	90.2	37.0	36.1	20.4	37.8
6	28.3	10.5	12.3	12.3	12.5
7	118.1	–	19.9	–	16.3
8	48.2	–	18.7	–	12.8
Mean	98.2	24.8	25.7	25.6	26.4
± 95% CL	± 35.0	± 10.3	±7.3	±9.5	±9.4
Mean Bioavailability	100%	26.6%	29.3%	27.1%	29.1%
± 95% CL		± 11.0%	±8.5%	±9.1%	±8.6%

Schedule A vs B/C/D/E: Significant ($P < 0.001$)
Schedule B vs C vs D vs E: Not significant

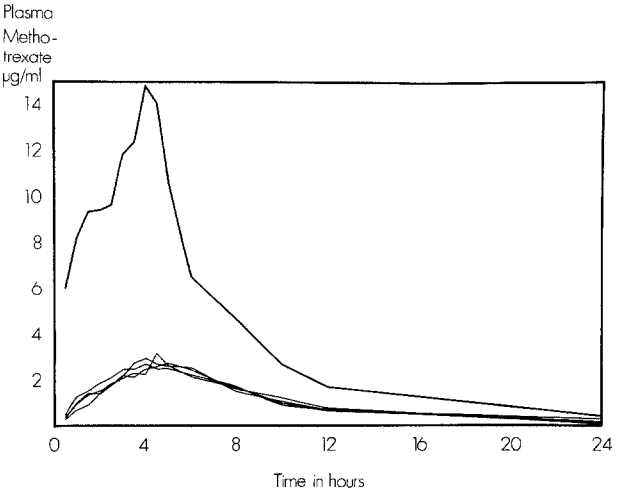

Fig. 1. The mean plasma concentrations of methotrexate in six patients following IV administration (———) or one of several oral schedules (———)

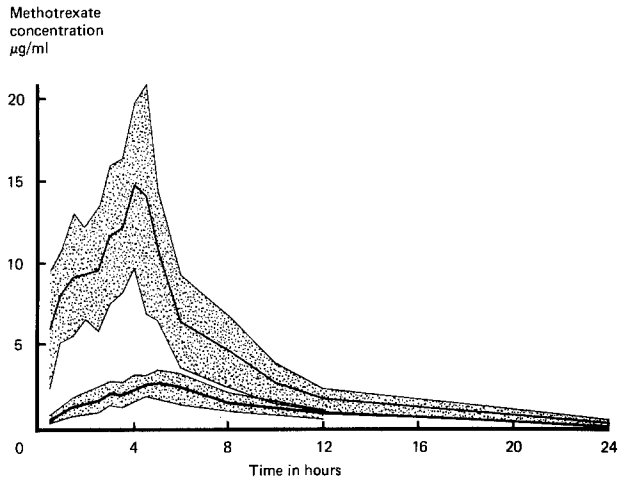

Fig. 2. The mean plasma concentrations of methotrexate together with 95% confidence limits *(stippled areas)* following IV infusion of 200 mg/m^2 over 4 h (———) or oral administration of 25 mg/m^2 every 30 min for eight doses (———)

Toxicity

The toxicity of MTX was minimal. One patient developed a sore mouth after IV (patient 2) and one after oral MTX given by schedules E and B (patient 6). Neither was unable to eat. All three episodes settled promptly. No patient experienced vomiting either before or after MTX administration, although antiemetic therapy was not used.

Discussion

The data presented here has shown poor bioavailability of MTX following oral administration. These results are in agreement with the findings of Henderson et al. [10], Wan et al. [21], and Smith et al. [18], but contradict the studies of Steele et al. [19] and Christophidis et al. [4], which had suggested improved [19] and almost complete [4] bioavailability following subdivision of the dose. No single-dose schedule was used in the study reported here. It is improbable that the MTX concentrations following a single-dose schedule would have been greater than those following the divided-dose schedules [4, 19], and these are clearly inadequate. The difference between this study and that of Christophidis et al. [4] is difficult to explain. In both studies a divided-dose schedule of oral MTX was compared directly with an IV infusion over the same period of time and the 25 mg/m^2 oral dose (individual dose range 35–50 mg) in schedules C, D, and E is similar in the two studies. Christophidis et al. [4] found a bioavailability of 87.6%, compared with less than 30% shown here. In the present study, although approximately double the dose was given over the first 4 h of study the mean peak plasma concentrations achieved after oral MTX were 50% lower. On the other hand, the peak plasma concentrations following IV MTX were more than double. The reason for this difference is not apparent, but the poor absorption shown in this study is in keeping with that in most reported studies [10, 18, 20, 21]. It is possible that the more frequent administration in our study (every 30 min compared with every hour) and the more prolonged administration in the study of Christophidis et al. [4] (16 h as against 4 h) may account partly for the difference. The demonstration that food significantly impairs the absorption of MTX [15] makes it necessary that patients are fasted for optimal absorption. It is clearly impractical to starve patients prior to therapy and for up to 16 h thereafter as in the study of Christophidis et al. [4].

The possibility that the impaired bioavailability was due to tablet formulation has been excluded by the demonstration that identical bioavailability was obtained with the syrup prepared from MTX injection BP. The plasma pharmacokinetics were similar irrespective of either the timing of oral MTX within the chemotherapy cycle or the duration of prior chemotherapy. This suggests that MTX absorption was impaired neither acutely (at day 10) by the other drugs in the chemotherapy regimen (etoposide, adriamycin, and vincristine), nor more chronically (1–4 months) by the complete regimen. Detailed studies of gastrointestinal function were not undertaken and more subtle impairment of absorption may have occurred. The gastrointestinal toxicity of this regimen was slight, being confined to short-lived nausea and vomiting after the initial part of the regimen (etoposide, adriamycin, and vincristine) only. It is unknown whether the absorption of MTX would have been affected in the presence of mucosal ulceration or other evidence of gastrointestinal toxicity.

These studies show that oral MTX at doses of 200 mg/m^2 is poorly absorbed, even in divided doses. It is unlikely, but possible, that further subdivision of the dose and perhaps an increase of the interval between doses would lead to improved absorption and hence to increased concentrations of MTX. Such regimens would become increasingly inconvenient for the patient. At this dose (200 mg/m^2) MTX should continue to be given IV for reliable effect.

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