Cancer Chemother Pharmacol (1983) 11:188–190

Cancer Chemotherapy and Pharmacology

Serum profiles and safety of intermediate-dose (500–1,000 mg) methotrexate following IV and IM administration

Barry M. Colls, Richard A. Robson, Bridget A. Robinson, and Gavin W. Tisch

Department of Medical Oncology, Christchurch Hospital, Private Bag, Christchurch, New Zealand

Summary. *Despite extensive clinical experience with methotrexate there is no consensus of opinion as to the ideal method of administration.*

This study tested the hypotheses that intermediate-dose (500–1,000 mg) methotrexate can safely be adminstered to outpatients as an IM injection, and that similar serum profiles of methotrexate result from IM and IV administration.

Fourteen patients received 500 mg methotrexate, and nine of these received 1,000 mg as an IM injection. Methotrexate levels at 24 and 48 h were below the levels at which toxicity can be expected.

Six patients received 500 mg both IM and IV and 1,000 mg both IM and IV. Serum methotrexate profiles over 48 h were similar following both IM and IV administration. This study showed no evidence of significant toxicity in terms of bone marrow, gastrointestinal, or renal impairment.

Introduction

Methotrexate was introduced into clinical practice in 1947 and since then has been the subject of numerous pharmacological studies. At first quite modest doses were used, but in recent years relatively massive doses, as high as 30,000 mg/m^2, have been administered [1]. When high doses are used parenteral administration is the preferred route, because of variable absorption from the gastrointestinal tract and first-pass metabolism [6]. On the other hand, within the lower dose range similar serum methotrexate profiles are obtained with PO, IV, and IM administration [4, 10].

High-dose IV methotrexate with folinic acid rescue has been intensively studied, and some workers hold the view that the potential hazards of this technique outweigh the potential therapeutic gains obtained by the high blood levels of methotrexate [5, 11]. In studies of more conventional parenteral dosage regimens (200 mg) it has been shown that the plasma levels of methotrexate at 24 h are not significantly different following IV or IM administration [2]. The current study tested the hypothesis that IM administration of intermediate-dose methotrexate (500–1,000 mg) with folinic acid rescue is nontoxic and results in a similar serum profile to that obtained after IV administration.

Reprint requests should be addressed to Dr. B. M. Colls

Patients and methods

Patients included in this study had failed primary therapy for advanced lymphoma or metastatic solid tumour, and were considered suitable for intermediate-dose methotrexate as a salvage regimen. Patients with significant renal impairment (creatinine clearance < 0.5 ml/s) or a third space (e.g., pleural effusion or ascites) were excluded because of the known alteration in pharmacokinetics associated with these conditions [1].

There were two groups of patients: The first group comprised 14 patients, whose age ranged between 28 and 68 years (mean 50 years, median 49 years). These patients received 500 mg, and nine of these subsequently received 1,000 mg, methotrexate IM. Serum levels of methotrexate were measured at 24 h and 48 h.

In the second group of six patients the age range was between 28 and 58 years (mean 45 years, median 47 years). They received the following injections of methotrexate: 500 mg IM, 500 mg IV, 1,000 mg IM, and 1,000 mg IV. There was an interval of at least 7 days between injections, and serum levels of methotrexate were measured at 1, 2, 3, 6, 12, 24, and 48 h.

Prior to each treatment two creatinine clearances were measured, and the serum creatinine was measured at 24 and 48 h.

Each 500 mg methotrexate (preservative-free) was reconstituted with 10 ml sterile water. The IV dose was administered as a slow bolus (< 5 min); the IM dose was injected deeply without local anaesthetic into one buttock. The 1,000 mg IM dose was administered as two divided 500 mg portions, each in 10 ml sterile water, one injection into each buttock.

Folinic acid rescue commenced at 24 h. With the 500-mg dose the rescue took the form of 7.5 mg folinic acid PO 6-h for 12 doses. With the 1,000-mg dose the dose of folinic acid was 15 mg PO 6-h for four doses, then 7.5 mg 6-h for a further 24 doses.

Alternative arrangements were made for IV fluids and parenteral folinic acid to be given if the patients were unable to maintain an adequate oral fluid intake (> 2 l/day) or were unable to take oral folinic acid. No other precautions, such as alkalinisation of the urine, were taken.

Methotrexate assay

A competitive binding assay was used, employing reagents supplied by the Enzyme Center, Boston USA. The assay was carried out according to the instructions, but the separation step was modified by aspirating the supernatant and counting the charcoal pellet [8].

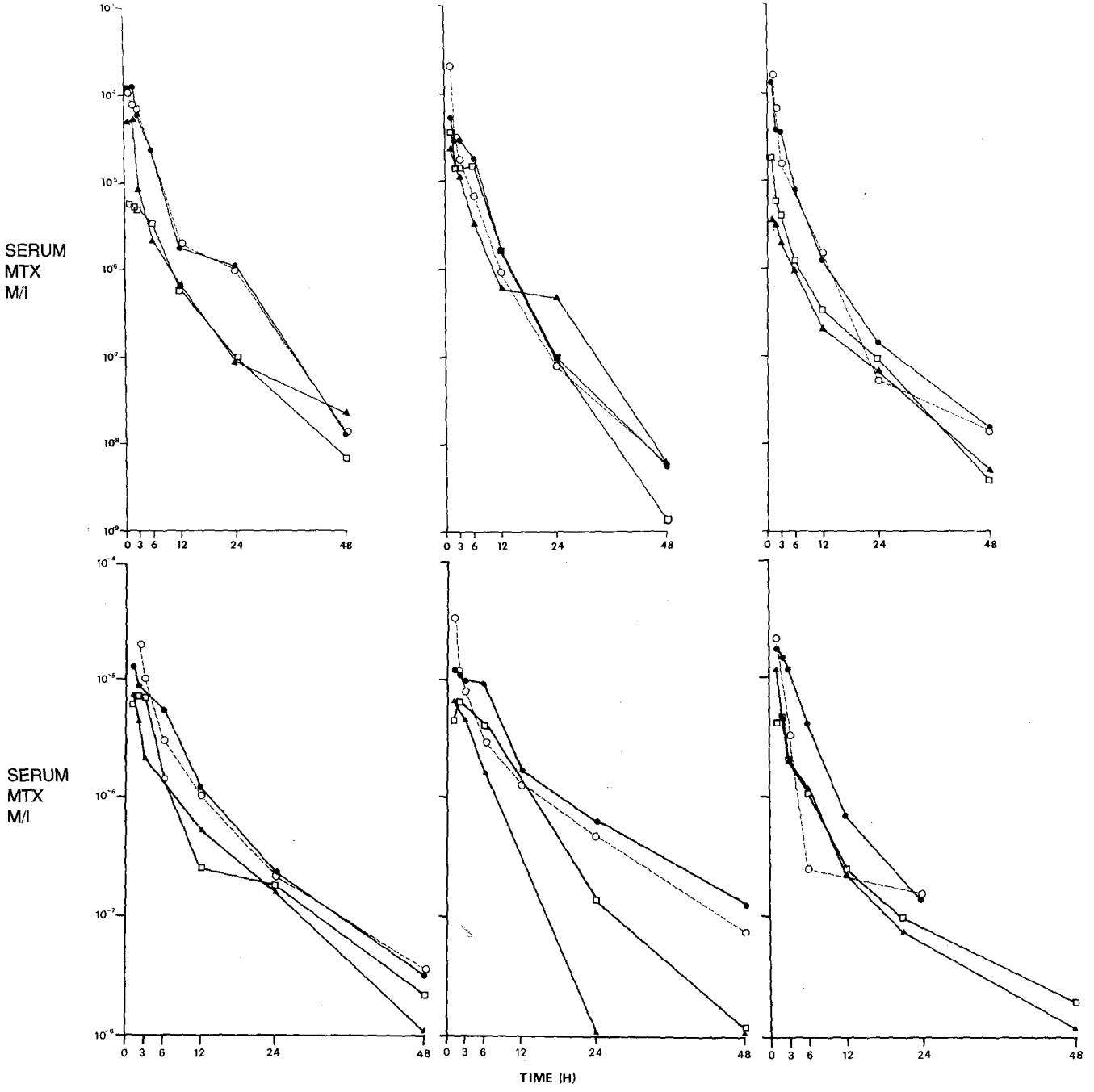

Fig. 1. Serum methotrexate (MTX) profiles in six patients after 500 mg IM (□---□), 500 mg IV (▲---▲), 1,000 mg IM (●---●), and 1,000 mg IV (○---○)

Results

Group 1

After 500 mg methotrexate IM the mean serum levels of methotrexate at 24 h and 48 h were 4.1×10^{-7} *M*/l ± 4.9×10^{-7} and 9.7×10^{-8} *M*/l ± 17×10^{-8}, respectively. After 1,000 mg methotrexate IM the mean serum levels at 24 h and 48 h were 5.5×10^{-7} *M*/l ± 6.3×10^{-7} and 4.7×10^{-8} *M*/l ± 4.4×10^{-8}, respectively.

Group 2

The serum methotrexate profiles of the six patients who received 500 mg both IM and IV or 1,000 mg IM and IV are shown in Fig. 1.

In five cases the IM route produced a lower peak level at 1 h than the IV route, followed by a slower decline in the serum methotrexate levels over the next 12 h. The rate of decline in the serum methotrexate levels after the first 12 h was similar for the IM and IV routes of administration.

Two patients showed evidence of reversible renal impairment, as detected by a change in the serum creatinine at 24 h and 48 h after a 1,000-mg IM dose. One episode of reversible renal impairment was caused by the patient's failure to maintain an adequate oral intake of fluid, and subsequently the serum creatinine returned to the pretreatment level. The second patient developed septicaemia. Following treatment of the septicaemia the renal function returned to the pretreatment level.

Haemoglobin, white cell count, and platelet count remained normal in all cases. One patient developed mouth ulceration, but no other patient developed evidence of mucositis. Although alternative arrangements were prepared to deal with hydration and other adverse reactions they proved necessary only once. The IM injections of methotrexate proved to be relatively painless and were completely acceptable to the patients.

Discussion

Despite a quarter of a century of clinical experience with methotrexate there is still no consensus of opinion as to the ideal dose or method of administration [1, 9]. Oral administration of high-dose methotrexate is not favoured, because of unpredictable absorption and first-pass metabolism. However, it has been shown recently that oral high-dose methotrexate given in divided doses produces similar serum levels to an IV infusion over the same time interval [3].

Various IV regimens, including bolus and bolus with infusion, have been used in attempts to increase the cytotoxicity and decrease the toxicity. There is still no apparent agreement as to the optimum method of IV administration.

IM administration of low-dose methotrexate has been shown to result in a similar serum level to PO and IV administration [2, 4].

In this study, IM methotrexate administration resulted in a similar serum profile to IV administration. Toxicity of methotrexate is related to the terminal phase of excretion [7]. Methotrexate levels at 24 h and 48 h were well below the accepted levels at which undue toxicity can be expected (1×10^{-5} *M*/l at 24 h and 1×10^{-6} *M*/l at 48 h [9]), and no patient developed any evidence of significant toxicity. The IM administration of methotrexate was acceptable to the patients and no local complications, such as soreness, abscess or ulceration were observed.

References

1. Bleyer WA (1978) The clinical pharmacology of methotrexate – new application of an old drug. Cancer 41: 36
2. Calvert AH, Bondy PK, Harrap KR (1977) Some observations on the human pharmacology of methotrexate. Cancer Treat Rep 61: 1647
3. Christophidis N, Vajda FJE, Lucas I, Moon WJ, Louis WJ (1979) Comparison of intravenous and oral high-dose methotrexate in treatment of solid tumours. Br Med J 1: 298
4. Freeman-Narrod M, Gerstley BJ, Engstrom PF, Barnstein RS (1975) Comparison of serum concentrations of methotrexate after various routes of administration. Cancer 36: 1619
5. Frei E, Blum RH, Pitman SW, Kirkwood JM, Henderson IC, Skarin AT, Mayer RJ, Bast RC, Garrick MB, Parker LM, Canellos GP (1980) High-dose methotrexate with leucovorin rescue. Rationale and spectrum of antitumour activity. Am J Med 68: 371
6. Henderson ES, Adamson RH, Oliverio VT (1965) The metabolic fate of tritiated methotrexate. II. Absorption and excretion in man. Cancer Res 25: 1018
7. Huffman DH, Wan SH, Azannoff DL, Hoogstraten B (1973) Pharmacokinetics of methotrexate. Clin Pharmacol Ther 14: 572
8. Myers CE, Lippman ME, Eliot HM, Chabner BA (1975) Competitive protein binding assay for methotrexate. Proc Natl Acad Sci USA 72: 3683
9. Paxton IW (1979) High-dose methotrexate therapy – an area of uncertainty. Aust NZ J Med 9: 722
10. Pinkerton CR, Welshman SG, Bridges IM (1982) Serum profiles of methotrexate after its administration in children with acute lymphoblastic leukaemia. Br J Cancer 45: 300
11. Woods RL, Fox RM, Tattersall MHN (1981) Methotrexate treatment of squamous cell head and neck cancers: dose response evaluation. Br Med J 282: 600

Received April 5, 1983/Accepted July 1, 1983