Pharmacokinetics of Small Doses of Methotrexate in Patients with Psoriasis

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The pharmacokinetics of methotrexate was studied in 23 patients with chronic plaque psoriasis. Ten patients received a single oral dose and 13 patients a single intramuscular injection of 25 mg methotrexate. Serum methotrexate was measured for 24 hours following administration of the drug using a magnetizable solid-phase radio-immunoassay. The disappearance of methotrexate from the serum fitted a two-compartment model with a distribution phase half-life of 1.18±0.12 h and an elimination phase half-life of 5.35±0.62 h following the oral dose and 1.45±0.22 h and 4.71±0.32 h, respectively following the intramuscular dose. Peak serum methotrexate concentrations varied greatly between patients but the mean area below the curve for the two routes of administration did not differ significantly. In a further 18 psoriatic patients receiving long-term maintenance methotrexate therapy there was no consistent relationship between salivary and serum methotrexate levels. (Received August 7, 1987.)

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Methotrexate is generally accepted as a useful second-line agent for the treatment of psoriasis unresponsive to conventional topical regimens (1). However, its use has been limited by the incidence of significant haematological and hepatic side effects. The mechanism of action of the toxic effects of methotrexate are poorly understood but appear to correlate with the frequency of administration, rather than with the actual dose of methotrexate (2), although there is some evidence that the cumulative dose of methotrexate is also important (3).

In an attempt to elucidate this matter further, a number of investigators have examined the pharmacokinetics of methotrexate. Burchenal et al. (4), using an enzymatic method, found that an oral dose of 5 mg methotrexate was absorbed within 60 min. Freeman (5), using a fluorimetric assay, reported a similar rapid and complete absorption following oral administration of up to 31 mg/m^2 of methotrexate, although absorption was incomplete at higher dosages (6).

Tattersall (7), measuring plasma levels following large doses of methotrexate by both an enzymatic method and by radio-immunoassay, reported a monophasic exponential decay with a median half-life of 5 1/2 h (8.1 h in patients exhibiting toxicity, 14.2 h in severe toxicity) whilst Calbert et al. (8) reported two phases of plasma disappearance with mean half-lives varying between 0.5 and 2.06 h for phase one and between 5.34 and 10.4 h for phase two. Huffman et al. (9), on the other hand, using a tritiated label, defined a triphasic disappearance curve with values of 0.75±0.11, 3.49±0.55 and 26.99±4.44 h respectively for phases one, two and three when 30 mg/m^2 was adminisered intravenously and serum levels of methotrexate were followed for 60 h, although the third phase was thought not to be due to intact methotrexate (10).

In view of these discrepancies and since much of the previous work was carried out with relatively large doses of methotrexate in neoplastic disease, the present study was designed to define the pharmacokinetics of smaller therapeutic doses in patients with recalcitrant psoriasis.

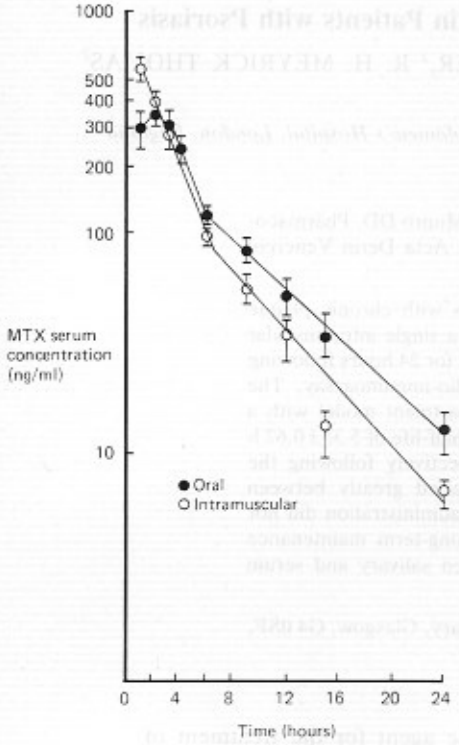

Fig. 1. Serum methotrexate (MTX) concentration following 25 mg oral (●—●) or intramuscular (○—○) methotrexate. Values are means ± SEM (p=0.60).

PATIENTS AND METHODS

Twenty-three patients, 11 women and 12 men, aged 45.4±3.1 years (range 18–72 years) with chronic plaque psoriasis took part in the study. Normal renal function was confirmed by 24-h urinary creatinine clearance. Each patient was admitted to hospital on the day of the study and was given a light breakfast only; all medications were discontinued for the week prior to admission. Patients were selected for oral or intramuscular therapy in random order. Ten patients were given 25 mg of oral methotrexate, the remaining 13 patients received 25 mg methotrexate by deep intramuscular injection into the right buttock. Blood was sampled from an antecubital vein at 1, 2, 3, 4, 6, 9, 12, 15, and 24 h following administration of the drug. The blood samples were separated and the sera kept at −20°C until analysis.

In a further 19 patients whose psoriasis was well controlled by long-term weekly oral methotrexate (maintenance dose 5–25 mg/week), simultaneous salivary and serum blood samples were collected 2 h after the weekly maintenance dose given by intramuscular injection into the right buttock. Five ml of saliva was collected from each patient in a sterile test tube without stimulation. Following homogenization by vortex mixing, the samples were centrifuged at 2 500 rpm for 10 min and the debris removed.

A I^{125} radio-immunoassay employing magnetizable solid-phase anti-methotrexate was used for the measurement of both salivary and serum levels of methotrexate (11). All measurements were made in duplicate.

Results are expressed as means ± standard error of the mean. Statistical comparison was made using the two-sample t-test.

RESULTS

Oral study

The serum concentration profile following both the oral and intramuscular dosages is shown in Fig. 1. Absorption following the oral dose was rapid, with peak serum methotrexate concentrations (295–648 ng/ml) being achieved by 1.6 h. A biphasic disappearance

was noticed, with the mean distribution phase half-life being 1.18±0.12 h and the mean elimination phase half-life 5.35±0.62 h. The mean area below the serum time curve (AUC) was 2216±262 ng h/ml (range 1040–3661 ng h/ml).

Intramuscular study

Absorption of methotrexate was faster following an intramuscular injection, with peak serum concentrations (270–968 ng/ml) reached within 1 h of the dose (Fig. 1). Disappearance of methotrexate from serum was again biphasic, with a mean distribution phase half-life of 1.45±0.22 h and an elimination phase half-life of 4.71±0.32 h. The mean AUC was 2417±277 ng h/ml (range 897–4510 ng h/ml). Although the mean serum concentration 1 h after intramuscular injection was higher than after a similar oral dose, the total AUCs were not significantly different ($p=0.60$).

Salivary MTX measurement

There was no consistent relation between the simultaneous salivary and serum concentrations of methotrexate in the 18 patients on long-term maintenance methotrexate (Table I). The ratio of salivary/serum methotrexate ranged between 0 and 18%.

DISCUSSION

The results of this study suggest that there is no significant difference in the absorption of methotrexate following either intramuscular or oral administration of 25 mg methotrexate and confirm the findings in a smaller study by Jones et al. (12). Similar peak concentrations of the drug were reached following both routes of administration, although the peak was reached more quickly following intramuscular injection. This is similar to the findings of a study measuring levels of methotrexate in erythrocytes which found identical erythrocyte methotrexate levels following both oral and intramuscular administration (13).

Table I. *Simultaneous salivary and serum levels of methotrexate (MTX)*

Patient	Weekly MTX dose (mg)	Salivary MTX concentration (ng/m)	Serum MTX concentration (ng/ml)	Ratio (%)
1	25	[a]	430	–
2	15	15.8	340	4.6
3	25	4.9	300	1.6
4	17.5	5.8	700	0.8
5	5	[a]	38	–
6	10	[a]	36	–
7	15	[a]	7	–
8	17.5	13.2	620	2.1
9	15	[a]	255	–
10	15	8.0	415	1.9
11	25	[a]	380	–
12	15	5.0	345	1.4
13	20	44.0	510	8.6
14	12.5	3.0	720	0.4
15	17.5	21.0	470	4.5
16	15	20.5	760	2.7
17	7.5	30.0	165	18.2
18	5	[a]	476	–

[a] Undetectable (below 1 ng/ml).

The inter-patient variation in methotrexate absorption as measured by the peak serum levels and the AUC is considerable. It is well known that patients with psoriasis have an increased incidence of a malabsorptive enteropathy (14). While this might account for a variation in absorption following oral administration, it would not explain the similarly wide inter-patient variation in the AUC and peak serum concentrations seen following intramuscular methotrexate. It is possible that differences in renal elimination and enterohepatic cycling of methotrexate could account for this variation in absorption. However, the wide inter-patient variation of serum methotrexate in the 18 patients on long-term maintenance methotrexate therapy (Table I) whose psoriasis was well controlled suggests that serum methotrexate is not a good indicator of the therapeutic effect of methotrexate in psoriasis.

A number of workers have demonstrated that methotrexate is excreted in saliva (15). Salivary measurements may reflect the unbound serum levels of therapeutic drugs (16) and may thus be used to monitor drug therapy. However, whilst the establishment of a correlation between serum and salivary methotrexate would have been useful, we have unfortunately been unable to determine any consistent correlation. We therefore conclude that maintenance therapy with methotrexate cannot be satisfactorily monitored by measurement of salivary drug levels.

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