Clinical Pharmacokinetics of Methotrexate

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Summary

The absorption of methotrexate following intramuscular injection and oral administration of small doses (<30mg/m²) is rapid and complete, whereas with oral doses in excess of 80mg/m² absorption is less than complete. Pretreatment with oral neomycin decreases and with kanamycin increases the gastrointestinal absorption of oral methotrexate.

The plasma disposition of methotrexate is multiexponential. Due to differences in sampling schedule and assay methods, widely varying estimates of elimination half-life (t½) of 6 to 69 hours of methotrexate have been reported. The long half-life may either be due to enterohepatic circulation of methotrexate and/or its metabolites or a slow elimination of dihydrofolate reductase (DHFR) bound methotrexate. The plasma clearance of methotrexate following small clinical doses is about 80ml/min, but may become saturated at high doses (20g). During high dose infusions, the peak plasma level is proportional to doses up to 200mg/kg.

Methotrexate is transported across cellular membranes via a carrier-mediated active process. At high concentrations, when the carrier route is saturated, passive diffusion assumes greater importance.

Methotrexate is not highly bound to plasma proteins (~50%). However, being highly ionised at physiological pH, the drug does not accumulate in the cerebrospinal fluid to any appreciable extent, necessitating intrathecal administration in the treatment of cerebral and meningeal metastases.

Renal excretion is the major route of elimination for methotrexate (~80%); the drug being actively secreted in the renal tubule by the general organic acid transport system. Hence, the renal clearance of methotrexate is decreased by the concomitant administration of organic acids, such as salicylate. The renal clearance of methotrexate is correlated with endogenous creatinine clearance which may provide a guideline to dosage adjustments according to renal function and age. With high dose methotrexate, routine administration of fluid and/or bicarbonate is recommended to prevent intratubular precipitation of the drug.

Biliary excretion of methotrexate constitutes less than 10% of the administered dose. Other extrarenal routes of excretion such as secretion into human breast milk and saliva are negligible.

About a third of an oral dose of methotrexate is metabolised by intestinal bacteria during absorption. The major metabolite is 4-amino-4-deoxy-N¹⁰-methylpteroyl acid. Small amounts (<11%) of 7-hydroxymethotrexate have also been found in urine of patients receiving high

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dose methotrexate therapy. Except for the polyγ-glutamates, all of the reported metabolites are less effective than methotrexate as an inhibitor of dihydrofolate reductase. As determined by inhibition of DNA synthesis, normal tissues are sensitive to low levels of methotrexate (∼10⁻⁷⁵M). Furthermore, toxicity with methotrexate is related to duration of exposure as well as to the dose or plasma concentration.

Impurities, such as methotrexate and other byproducts of the synthetic process have been found in commercial parenteral dosage forms of methotrexate. The clinical significance of these impurities requires further study.

For a phase-specific chemotherapeutic agent such as methotrexate, effective plasma levels of the drug should be maintained during the proliferative phase of the tumour cell cycle to achieve a maximum cytotoxic effect. Monitoring the plasma level of methotrexate, particularly during high dose therapy, may provide information regarding impending toxicity and the need for extended citrovorum factor rescue.

Folic acid antagonists were introduced in 1948 by Farber and his associates for the treatment of acute leukaemia. Since then methotrexate (amethopterin, 4-amino-N¹⁰-methyl-pteroylglutamic acid; fig. 1), has been used with varying degrees of success to treat many other types of cancer. Recently, improved responses in the treatment of tumours previously considered resistant to methotrexate have been attained by the use of large doses in combination with citrovorum factor (leucovorin, folinic acid, N₂-formyl-tetrahydrofolate) rescue (Jaffe et al., 1974; Djerassi et al., 1972; Capizzi et al., 1970).

Methotrexate exerts its cytotoxic effect by binding irreversibly to the enzyme, dihydrofolate reductase (DHFR), decreasing tetrahydrofolate and, thus, biosynthesis of deoxyribonucleic acid, ribonucleic acid and cellular proteins. The development of resistance to the antitumour effect of methotrexate has been an obstacle to its successful therapeutic use. Resistance has been attributed to increased levels of DHFR or to decreased permeability of the tumour cells to methotrexate (Goldman, 1971). Raising the dose to overcome the resistance may be effective, but is inevitably accompanied by an increased risk of severe host toxicity. Citrovorum factor supplies the product of the inhibited reductase enzyme, alleviating the folate depletion induced by methotrexate. In tumour bearing mice, the efficacy of aminopterin was increased with reduced host toxicity when citrovorum factor was administered subsequent to the antifolate (Goldin et al., 1954). The administration of this normal metabolite selectively rescues normal tissues from the lethal effects of methotrexate without neutralising all antitumour activity. The full potential of citrovorum factor rescue was not fully exploited in humans until Djerassi undertook high-dose methotrexate therapy (Djerassi, 1975).

There has been renewed interest in the clinical pharmacology of methotrexate as a result of the reported success of high dose therapy. The clinical pharmacokinetics of methotrexate are reviewed in this article and areas where further research would improve our understanding and use of methotrexate therapy outlined.

1. Pharmacokinetic Properties

As a result of the availability of sensitive, accurate analytical methods and our increasing awareness of pharmacokinetic principles in experimental design, a more definite picture of the pharmacokinetics of methotrexate has emerged in recent years.

1.1 Absorption

1.1.1 Intramuscular Administration

Absorption following intramuscular injection of methotrexate is rapid and complete (Freeman-Narrod et al., 1975). The gradual absorption of drug from the intramuscular site offsets the rapid fall in serum levels seen during the initial distribution phase.