Pharmacokinetics of Trimetrexate (NSC 352122) in Monkeys

Frank M. Balis,1 Cynthia M. Lester, and David G. Poplack

Pediatrie Branch, National Cancer Institute, NIH, Bethesda, Maryland 20892

ABSTRACT

The pharmacokinetics of trimetrexate was studied in Rhesus monkeys following i.v. bolus, continuous i.v. infusion, oral, and subcutaneous administration. Two methods were used to measure drug concentration in plasma, cerebrospinal fluid (CSF), and urine: the dihydrofolate reductase inhibition assay, and a reverse phase high-pressure liquid chromatography assay. The pharmacokinetic behavior of trimetrexate was characterized by triexponential plasma disappearance, elimination primarily by biotransformation, substantial plasma protein binding, poor CSF penetration, and limited oral bioavailability. Methotrexate, administered in an equimolar dose for comparison, was cleared more rapidly from plasma than was trimetrexate. Trimetrexate concentration remained above 0.1 µM 3-fold longer. In contrast to methotrexate, which is cleared almost exclusively by renal excretion, renal clearance of trimetrexate accounted for <5% of total clearance. A significant discrepancy was observed in plasma and urine trimetrexate concentrations measured by the two assay methods. The dihydrofolate reductase inhibition assay gave results approximately 2- to 4-fold higher in plasma. Two metabolites of trimetrexate which inhibit dihydrofolate reductase were identified in urine (one was also found in plasma) and appear to account for the different results obtained by the two assays. These metabolites would probably also interfere with the competitive protein binding assay currently being used to measure trimetrexate in ongoing phase I trials.

INTRODUCTION

Trimetrexate (2,4-diamino-5-methyl-6-[(3,4,5-trimethoxyanilino) methyl]quinazoline) is a new folate antagonist which is currently undergoing phase I clinical testing. Like methotrexate, the classical antifolate, trimetrexate is a potent inhibitor of the enzyme dihydrofolate reductase (1). However, the mechanism of cell entry and intracellular metabolism of trimetrexate and methotrexate apparently differ (2-4). Trimetrexate also has a broader range of antitumor activity in vivo against murine tumors than does methotrexate (5). As has been demonstrated previously for methotrexate (6), the antitumor activity of trimetrexate in vivo against P388 leukemia is markedly schedule-dependent with more prolonged exposures to the drug producing a greater effect (5).

The biochemical pharmacology and pharmacokinetics of methotrexate have been studied extensively, and the application of this knowledge has resulted in the safer and more efficacious use of methotrexate. Although some of these principles may also be applicable to the clinical use of trimetrexate, differences in structure, metabolism, mechanisms of resistance, and spectrum of antitumor activity suggest these agents may not be totally comparable. In the present study the pharmacokinetics of trimetrexate in the subhuman primate was examined and contrasted to the pharmacokinetics of methotrexate in the same species. Significant differences in the route of elimination, rate of clearance, and volume of distribution were observed. In addition, metabolites of trimetrexate capable of inhibiting dihydrofolate reductase were detected.

MATERIALS AND METHODS

Drug. Trimetrexate glucuronate was obtained from the Drug Development Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD and was supplied in 10-ml vials, each containing 50 mg. This was reconstituted in 1.9 ml sterile water (25 mg/ml) for administration to the monkeys. Trimetrexate acetate which was used in making standards for the HPLC2 and dihydrofolate reductase inhibition assays was also obtained from the Drug Development Program, National Cancer Institute. 14C radiolabeled trimetrexate isethionate (specific activity, 25.5 µCi/mg) was obtained from Warner-Lambert, Ann Arbor, MI. The radio-labeled carbon was in the middle methoxy group of the trimethoxynoline ring. Prior to administration of the 14C-labeled trimetrexate to two monkeys, it was diluted with cold trimetrexate glucuronate to a specific activity of 1.8 µCi/mg and filtered through a 0.22-µm filter. The purity of both the acetate salt and the 14C-labeled trimetrexate was >98% by HPLC.

Monkeys. Adult male rhesus monkeys (Macaca mulatta) ranging in weight from 6.7 to 11.7 kg were used in these experiments. The animals were housed individually and received food and water ad libitum (except prior to an oral dose, in which case animals were fasted overnight). Blood samples were drawn from a saphenous or femoral venous catheter opposite from the site of drug administration. CSF samples were obtained from a chronically indwelling Pudenz catheter attached to a s.c. implanted Ommaya reservoir (7).

Experiments. The pharmacokinetics of trimetrexate was studied following i.v. bolus and continuous i.v. infusion dosing schedules and following administration by the oral and subcutaneous routes. Three monkeys received an i.v. bolus dose of 100 mg/m2 m dose. Blood samples were collected in heparinized tubes prior to administration and 5, 15, and 30 min and 1, 2, 3, 4, 6, 8, 12, and 24 h after the dose. Plasma was separated immediately by centrifugation and frozen at -20° until assayed. Except for the 5-min sample, CSF was collected from the Ommaya reservoir simultaneously with blood samples and frozen at -20°. The reservoir was pumped four times before and after each sample to ensure adequate mixing with ventricular CSF.

The oral bioavailability of trimetrexate was studied in three animals. Each received the 30 mg/m2 dose as an i.v. bolus and, in a second experiment via a nasogastric tube with the order of administration randomized. Blood sampling times were identical to those listed above for the 100 mg/m2 dose with additional samples obtained at 45 and 90 min following the dose. Two of these animals, each given the 30 mg/m2 i.v. bolus dose received 14C-labeled trimetrexate. These two animals also had all urine and stool collected and frozen over 72 h following the dose in 24-h aliquots.

A continuous i.v. infusion was administered to three monkeys at a

Received 5/14/85; revised 8/8/85; accepted 10/2/85.

1 To whom requests for reprints should be addressed, at Bldg. 10, Room 13N240, Pediatric Branch, National Cancer Institute, NIH, Bethesda, MD 20892.

2 The abbreviations used are: HPLC, high-pressure liquid chromatography; DHFR INH, dihydrofolate reductase inhibition; AUC, area under the curve; conc., concentration; CLβ, total body clearance; CSF, cerebrospinal fluid.
dose of 10 mg/sq m/hr, which was calculated to achieve a steady state plasma level of 5 \(\mu M\) using clearance values obtained from the i.v. bolus experiments. Prior to the 8-h infusion each animal received an i.v. bolus loading dose of 40 mg/sq m. Blood samples were collected prior to the dose and 0, 15, and 30 min and 1, 2, 4, 6, 8, 12.25, 12, and 24 h after the start of the infusion. CSF sampling times were 0, 1, 2, 4, 6, and 8 h. The same three animals also received a subcutaneous dose of 125 mg/ sq m, which was approximately equal to the total dose given by infusion. Blood sampling times were identical to those for the i.v. infusion.

All animals received leucovorin 24 and 48 h after each dose of trimetrexate. No significant toxicity was noted in any of the animals with this regimen.

For comparison, plasma and CSF were monitored in three monkeys following a 34 mg/sq m dose of methotrexate administered as an i.v. bolus. Blood and CSF samples were obtained at 0, 15, and 30 min and 1, 2, 3, 4, 6, 8, and 12 h after the dose. The samples were otherwise handled in the same manner as described for trimetrexate.

Sample Analysis. Trimetrexate in plasma, CSF, and urine was measured by two methods, the DHFR INH assay described previously for methotrexate (8) and a HPLC assay. The DHFR INH assay was also used to measure methotrexate in the plasma and CSF of the three monkeys receiving this drug. The DHFR INH assay did not require modification to measure trimetrexate. The lower limit of sensitivity with the DHFR INH assay is 0.005 \(\mu M\) for trimetrexate and 0.001 \(\mu M\) for methotrexate. The coefficient of variation for within run and day-to-day replicates is <10% for both drugs.

Plasma samples and standards (1.0 ml) to be measured for trimetrexate by HPLC were spiked with \(^{[14]C}\)trimetrexate as an internal standard and applied to a C18 SEP-PAK cartridge (Waters Associates, Milford, MA). After a 3-ml water wash, the trimetrexate was eluted with 2 ml acetonitrile, and the eluant was evaporated to dryness under a nitrogen stream. The residue was reconstituted in 0.2 ml of mobile phase, resulting in a 5-fold concentration of the original 1.0 ml plasma sample. The recovery with this sample preparative technique was 71 ± 8% (SD). The HPLC system used consisted of a Waters model 680 automated gradient controller with two model 510 pumps and a U6K injector (Waters Associates). The column was a 10-\(\mu m\) C18 Radial-Pak cartridge used in a Z-module radial compression separation system (Waters Associates). The eluant was monitored with a Beckman 165 dual channel, variable wavelength detector (Beckman Instruments, Inc., Berkeley, CA) at a wavelength of 240 nm. The mobile phase was 0.01 M KH2PO4 buffer, pH 7.5, with 40% acetonitrile with a flow rate of 2.5 ml/min. The elution time for trimetrexate under these conditions was 12.5 min. With the 5-fold concentration of the samples, the lower limit of sensitivity is 0.05 \(\mu M\). The coefficient of variation for replicates is <10%. Plasma standards for the HPLC assay were measured with the DHFR INH assay to ensure comparability of the two methods.

The plasma samples from the monkeys given \(^{[14]C}\)trimetrexate had to be assayed under different conditions, since the 14C already present in plasma would interfere with using \(^{[14]C}\)trimetrexate as an internal standard. Instead, 0.2 \(\mu M\) of trimethoprim (Sigma Chemical Co., St. Louis, MO) was added as an internal standard to each sample prior to extraction on the SEP-PAK. In addition, a 5-\(\mu M\) Nova-Pak C18 Radial-Pak cartridge (Waters Associates) with a mobile phase of 0.02 M KH2PO4 buffer, pH 4.5, with 23% acetonitrile at a flow rate of 2 ml/min replaced the 10-\(\mu M\) column and mobile phase described above. The retention times for trimethoprim and trimetrexate are 3 and 5.8 min. This is a more rapid and convenient technique for future studies. Plasma was screened for the presence of metabolites using the 5-\(\mu M\) Nova-pak column and a mobile phase of 0.01 M KH2PO4 buffer, pH 7.5, with 12% acetonitrile at 2 ml/min.

Urine from the two monkeys receiving radiolabeled drug was centrifuged and injected directly onto the 10-\(\mu M\) C18 Radial-Pak column. The mobile phase was 0.01 M KH2PO4 buffer, pH 5.0, at 2 ml/min with a linear gradient of acetonitrile from 0 to 60% over 25 min. Fractions were collected and measured with the DHFR INH assay and counted in a Beckman LS 8100 scintillation counter (Beckman Instruments). A fraction eluting before trimetrexate which inhibited DHFR was collected, hypohydrated, reconstituted in a small amount of mobile phase and reinfected onto the 10-\(\mu M\) C18 column with a mobile phase of 0.01 M KH2PO4 buffer, pH 7.5, with 12% acetonitrile at 2 ml/min. The eluant was monitored with the UV detector at 240 nm and fractions were again collected for the DHFR INH assay and counting for 14C.

The 72-h stool collection was homogenized in 3 volumes of water. An aliquot was centrifuged, and the supernatant was counted for 14C. Counts per minute for all radiolabel studies were corrected for quench using the H# technique (9).

**Plasma Protein Binding.** Fresh plasma from a normal monkey was spiked with trimetrexate glucuronate to a final concentration of 5 \(\mu M\) and placed in one chamber of a dialysis cell (Technilab Instruments, Pequannock, NJ). An equal volume of phosphate-buffered saline, pH 7.2 (Biofluids, Rockville, MD), with 0.01% sodium azide was added to the other chamber. The two chambers were separated by a regenerated cellulose dialysis membrane (Technilab Instruments). Dialysis was performed at 37°C with gentle shaking for 16 h. At the end of the incubation an aliquot from each chamber was assayed using the DHFR INH assay. The percentage of drug bound was equal to:

\[
\text{Plasma concentration} - \text{buffer concentration} \times 100
\]

**Pharmacokinetic Analysis.** Plasma concentration-time data from the i.v. bolus experiments were fitted to both biexponential (\(n = 2\)) and triexponential (\(n = 3\)) equations,

\[
C(t) = \sum_{i=1}^{n} A_i e^{-k_i t}
\]

using MLAB, a nonlinear curve fitting program (10). Akaike’s information criterion (11) was used to determine which equation best fitted the data. The half-life for each phase of elimination was calculated by dividing 0.693 by the rate constant (\(k_i\)) for that phase. Other pharmacokinetic parameters were calculated using model-independent methods. The AUC was derived by the linear trapezoidal method (12), and extrapolated to infinity by adding the quotient of the final plasma concentration divided by the terminal rate constant (\(k_t\)). CL was the dose divided by the AUC, and renal clearance equaled the amount excreted in urine over 72 h divided by the AUC. In the monkeys receiving trimetrexate by continuous infusion, CL was estimated by dividing the infusion rate by the steady state concentration in plasma. The volume of distribution at steady state was calculated from the area under the moment curve (13).

The fraction of drug penetrating into the CSF was derived from the ratio of the AUCs in CSF and plasma for the i.v. bolus dose and the ratio of steady state concentration in CSF and plasma for the continuous i.v. infusion. Bioavailability of the oral dose was the ratio of the AUC following the oral dose and the AUC following the same dose given by i.v. bolus.

**RESULTS**

**Pharmacokinetics.** The plasma disappearance of trimetrexate following an i.v. bolus dose (Chart 1) was best fitted by a triexponential equation. The half-lives and other pharmacokinetic parameters calculated from the i.v. bolus doses are listed in Table 1. Plasma concentrations measured by the more specific HPLC assay were lower than those obtained with the DHFR INH assay after the initial time points, which suggests the presence of one or more circulating metabolites of trimetrexate capable of inhibiting DHFR (Chart 1). The values for pharmacokinetic parameters calculated from plasma concentrations measured by the two techniques were also significantly different (Table 1). Plasma
and CSF trimetrexate concentrations measured by the DHFR INH assay and reported as µM actually represent trimetrexate plus unknown concentrations of DHFR inhibiting metabolites.

Chart 2 and Table 1 show the comparison between trimetrexate and methotrexate administered in approximately equimolar doses. Methotrexate is cleared more rapidly from plasma and has a smaller volume of distribution at steady state. The plasma concentration of trimetrexate remains above 0.1 µM [the concentration at which methotrexate and trimetrexate produced >90% inhibition of cell growth in vitro against a human lymphoblastic leukemia cell line (3)] 3 times longer than does that of methotrexate. The route of elimination also appears to be different. Renal clearance of trimetrexate accounts for only a small fraction of CLTMB, which indicates that trimetrexate is cleared primarily by biotransformation, in contrast to methotrexate, which is known to be cleared almost exclusively by renal excretion in humans (14). Despite its greater lipophilicity, trimetrexate does not penetrate into the CSF to any greater extent than does methotrexate (Chart 3 and Table 1).

When administered as a 10 mg/sq m/h continuous i.v. infusion, trimetrexate achieved a steady state concentration in plasma of $3.32 \pm 0.51 \text{ µM}$ by HPLC ($5.75 \pm 0.48 \text{ µM}$ by DHFR INH).

Estimates of CLTMB calculated from this plasma steady state concentration was $138 \pm 22 \text{ ml/min/sq m}$. The ratio of steady state concentration in CSF to plasma was $0.029 \pm 0.029$ (DHFR INH assay). These values are in close agreement to those obtained from the i.v. bolus doses (Table 1).

Chart 4 is a comparison between plasma levels following the 8-h i.v. infusion and the s.c. dose. The s.c. dose resulted in a slow release of trimetrexate that simulated the infusion and provided a more prolonged exposure to the drug than an i.v. bolus dose.

Results of the oral bioavailability study are shown in Chart 5. The fraction of parent drug absorbed unchanged into the systemic circulation was only $0.23 \pm 0.05$ (HPLC method). There was a greater discrepancy in plasma concentration and AUC between assay methods with the oral dose than the i.v. dose (Table 2). Following the oral dose trimetrexate (unchanged), as measured by the HPLC assay, accounts for only one-fourth to one-fifth of the DHFR inhibiting activity in plasma, while following an i.v. dose it accounts for one-half of the DHFR inhibiting activity in plasma.

### Protein Binding Studies

Trimetrexate was $90 \pm 1\%$ bound to plasma proteins at a concentration of $5 \text{ µM}$, as measured by the equilibrium dialysis method. Ninety-three % of the drug

---

**Table 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/m²)</th>
<th>No.</th>
<th>Assay</th>
<th>AUC²⁰⁺ (µM-min)</th>
<th>AUC²⁰⁺⁺ (µM-min)</th>
<th>CSF-P</th>
<th>CL⁻⁰⁺ (ml/min/m²)</th>
<th>Cl⁻⁰⁺⁺ (ml/min/m²)</th>
<th>Vdav (liters/m²)</th>
<th>Half-lives (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimetrexate</td>
<td>100</td>
<td>3</td>
<td>H</td>
<td>2262 ± 486²</td>
<td>142 ± 151</td>
<td>0.034 ± 0.029</td>
<td>123 ± 24</td>
<td>23.7 ± 3.3</td>
<td>17.8 ± 1.7</td>
<td>3.3 ± 0.8</td>
</tr>
<tr>
<td>Trimetrexate</td>
<td>30</td>
<td>3</td>
<td>H</td>
<td>596 ± 173</td>
<td>8.4 ± 3.9</td>
<td>0.021 ± 0.008</td>
<td>194 ± 21</td>
<td>9.5 ± 2.4</td>
<td>6.3 ± 2.0</td>
<td>26 ± 162</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>34</td>
<td>3</td>
<td>D</td>
<td>365 ± 39</td>
<td>8.4 ± 3.9</td>
<td>0.021 ± 0.008</td>
<td>194 ± 21</td>
<td>9.5 ± 2.4</td>
<td>6.3 ± 2.0</td>
<td>26 ± 162</td>
</tr>
</tbody>
</table>

* P, plasma; CL, renal clearance; Vdav, volume of distribution at steady state; H, HPLC assay; D, DHFR INH assay.

* Mean ± SD.

* n = 2.
initially present in the plasma was recovered from the plasma and buffer at the end of the incubation.

Metabolism Studies. In an attempt to evaluate trimetrexate metabolism, two monkeys received \(^{14}\)C-labeled trimetrexate. Over the 72 h following drug administration, only 16% of the total dose of \(^{14}\)C administered was recovered in urine, and only 1% was found in the stool. Plasma clearance of total \(^{14}\)C was biexponential, with an initial half-life of 3.7 min, which is similar to the initial half-life of the parent compound. However, the terminal \(^{14}\)C half-life of 1030 min was much longer than the terminal half-life of trimetrexate.

Chart 6 shows the chromatograms of urine from the two monkeys receiving \(^{14}\)C-labeled trimetrexate. Six to seven peaks of radioactivity are present, one representing trimetrexate at 40 min. Two peaks of DHFR inhibiting activity were also present in urine, one corresponding to the parent drug (40 min) and a larger peak at 18 min, apparently representing a more polar metabolite(s) of trimetrexate. This peak was not present in urine collected before or 6 days after the dose. The metabolite peak does not coelucent with a peak of radioactivity, which suggests that the middle methoxy group containing the \(^{14}\)C has been demethylated.

This peak containing DHFR inhibiting material (fraction 18) was collected, lyophilized to dryness, reconstituted in a small amount of mobile phase, and reinjected under conditions described in "Materials and Methods," yielding the chromatogram shown in Chart 7. Two peaks can be detected by DHFR INH assay of eluant fractions and by monitoring UV absorption at 240 nm that are not present in baseline urine samples. There was no radioactivity associated with either peak. These peaks apparently represent metabolites of trimetrexate that are capable of inhibiting DHFR (the metabolites inhibit both Lactobacillus casei and bovine DHFR).

Plasma was also screened for the presence of metabolites. Chart 8 shows chromatograms of extracted plasma prior to the dose and at serial time points after the dose in a monkey receiving an i.v. bolus dose. Two peaks which only appeared after trimetrexate was administered can be identified. One eluted at 4.5 min, corresponding to one of the DHFR inhibiting metabolites seen in urine. The second peak at 5.9 min had no detectable DHFR inhibiting activity associated with it and may represent an inactive metabolite. A very small peak is seen in the chromatogram at the time (7.3 min) the second DHFR inhibiting metab-
Comparison of area under the plasma concentration time curve following i.v. and oral dosing and peak plasma levels following oral dosing, using both assay methods to measure plasma concentration

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Dose (mg/sq m)</th>
<th>AUC (µM-min)</th>
<th>Peak plasma concentration (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>i.v. 30</td>
<td>DHFR INH</td>
<td>HPLC</td>
</tr>
<tr>
<td></td>
<td>i.v. 30</td>
<td>999 ± 103</td>
<td>596 ± 173</td>
</tr>
<tr>
<td></td>
<td>p.o. 30</td>
<td>499 ± 120</td>
<td>128 ± 13</td>
</tr>
</tbody>
</table>

*Mean ± SD.

The purpose of this study was to define the pharmacokinetic behavior of trimetrexate in a subhuman primate model which has previously been predictive of drug kinetics in humans (15). Trimetrexate pharmacokinetics in this model were characterized by triexponential plasma disappearance, clearance primarily by biotransformation, poor CNS penetration, substantial plasma protein binding, and limited oral bioavailability.

The metabolism of trimetrexate appears to be complex, with both inactive and DHFR inhibiting metabolites identified in plasma and urine. Although the exact structure of these metabolites has yet to be determined, it appears that one step in the metabolic pathway is the demethylation of the middle methoxy group on the trimethoxyaniline ring. The loss of this single carbon fragment from the trimetrexate molecule and its subsequent incorporation into other molecules or excretion via the lungs probably accounts for the loss of over 80% of the radiolabel and the more prolonged terminal half-life of 14C in plasma. Demethylation appears to be a major step in the degradative metabolism of trimetrexate. Since the 14C was cleaved from trimetrexate, the multiple peaks of radioactivity found on chromatography of urine probably do not all represent metabolites of trimetrexate but rather incorporation of the 14C into other compounds. The metabolites identified were more polar than trimetrexate based on their shorter retention on the reversed-phase columns.

Even though the two metabolites inhibit DHFR, it cannot be concluded that they are active metabolites until cytotoxicity studies are performed. Since they appear to be more polar than trimetrexate, they may not gain entry into cells as readily. Further purification and characterization of these metabolites are ongoing.

The metabolites identified in urine and plasma, which are capable of inhibiting DHFR, interfere with the DHFR INH assay and presumably would also interfere with the competitive protein binding assay (16), which uses DHFR as the binding protein. As a result, plasma and urine levels are falsely high, and pharmacokinetic parameters calculated from these levels are incorrect. The HPLC method appears to be more specific. When interpret-

![Chart 6](chart6.png)

![Chart 7](chart7.png)

![Chart 8](chart8.png)
ing or comparing pharmacokinetic data from ongoing phase I trials, the method of measuring trimetrexate must be considered.

The disposition kinetics of trimetrexate and methotrexate differ significantly in the monkey. Trimetrexate is cleared more slowly and, with an equivalent dose, may therefore provide a more prolonged drug exposure. The primary route of elimination of the two drugs is also different. While methotrexate is excreted almost exclusively by the kidneys (14), the renal clearance of trimetrexate accounts for <5% of the total clearance. If trimetrexate is found to have significant antitumor activity, it may be useful in patients with renal dysfunction in place of methotrexate.

As in the present study in monkeys, Weir et al. (17) have reported relatively low CSF drug concentrations following systemic administration in dogs. Trimetrexate was originally synthesized to be a lipid soluble antifol, and thus it was anticipated that trimetrexate would penetrate into the CSF to a greater extent than methotrexate [the log of the partition coefficient for trimetrexate in octanol versus water is 0.88 compared to -1.85 for methotrexate (18)]. One explanation for its limited central nervous system penetration in monkeys may be the high percentage of circulating trimetrexate bound to plasma protein. In contrast, protein binding of trimetrexate in dogs was reported to be negligible when measured by a size exclusion column technique (17). This marked difference in results is more likely to be due to differences in techniques used to measure protein binding than species differences. Our study used the classical equilibrium dialysis method, which is not affected by nonspecific drug binding within the system.

Using the DHFR INH assay, Weir et al. (17) reported a high bioavailability of 80% following an oral dose in dogs. In our study with the more specific HPLC assay, the bioavailability in monkeys was considerably lower. This difference is in large part due to the more extensive metabolism of trimetrexate to DHFR-inhibiting metabolites following an oral dose. This phenomenon is probably a result of presystemic or first pass metabolism of trimetrexate in the liver or intestinal mucosa.

The slow-release effect following subcutaneous administration of trimetrexate simulated the levels achieved with an 8-h continuous i.v. infusion. Since the duration of exposure to antifol is a significant factor in producing cytotoxic effect, this convenient route of administration could provide an alternative to prolonged intravenous infusions.

REFERENCES


Pharmacokinetics of Trimetrexate (NSC 352122) in Monkeys

Frank M. Balis, Cynthia M. Lester and David G. Poplack


Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/46/1/169

Sign up to receive free email-alerts related to this article or journal.

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.