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# Pediatric Phase I Trial and Pharmacokinetic Study of Piritrexim Administered Orally on a Five-Day Schedule

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## ABSTRACT

**Piritrexim, a new nonclassical antifolate, was evaluated in a multiinstitutional phase I trial in children. The starting dose was 290 mg/m²/day, administered p.o. every 12 h for 5 consecutive days, with courses repeated every 21 days. Dose reduction, initially to 200 mg/m²/day and subsequently to 140 mg/m²/day, was required because dose limiting myelosuppression and mucositis were encountered at the 290- and 200-mg/m²/day dose levels. Non-dose limiting toxicities included transient elevations in liver function tests, mild nausea, and skin rashes. The maximum tolerated dose was 140 mg/m²/day for 5 days. Pharmacokinetic monitoring was performed at steady state during the first course. For the 140-, 200-, and 290-mg/m²/day dose groups, the mean ± SE peak plasma concentrations were 5.3 ± 0.84, 9.3 ± 1.7, and 10.2 ± 2.3 μM, respectively, and occurred at a median of 1.5 h following the p.o. dose. The mean area under the plasma concentration-time curves were 18.1 ± 2.3, 45.4 ± 8.9, and 56.9 ± 16.3 μM·h, respectively. Absolute bioavailability in two patients who were also monitored following a single i.v. dose of 140 and 200 mg/m²/day of piritrexim was 35 and 93%, respectively. Dose limiting toxicities were observed in 9 of 10 patients with 12-h trough piritrexim concentrations >0.5 μM, whereas only 2 of 7 patients with trough concentrations <0.5 μM experienced dose limiting toxicities. A limited pharmacokinetic sampling strategy that allowed the area under the plasma concentration-time curve to be accurately predicted from the 3- and 6-h plasma drug concentration was developed. The recommended dose for future phase II trials is 140 mg/m²/day administered p.o. every 12 h for 5 consecutive days. Pharmacokinetic monitoring at 3, 6, and 12 h postdose may be useful for estimating bioavailability and for predicting which patients are at greatest risk for developing toxicity.**

## INTRODUCTION

Piritrexim [2,4-diamino-6-(2,5-dimethoxybenzyl)-5-methylpyrido[2,3-*d*]pyrimidine, BW301U] is a p.o. administered, lipid soluble antifolate which, like methotrexate, is a potent inhibitor of dihydrofolate reductase (1). However, it differs from methotrexate in its mechanism of cell entry and intracellular metabolism. Piritrexim appears to rapidly enter cells by passive diffusion (2), in contrast to methotrexate, which is dependent on cell-mediated transport. Because piritrexim lacks the glutamate residue found on methotrexate and naturally occurring folates, it is not polyglutamated intracellularly. Piritrexim, therefore, may be able to circumvent resistance to methotrexate that is based on a transport defect or on decreased polyglutamation.

In the *in vitro* human tumor cell cloning assay, the antitumor activity of piritrexim compared favorably with that of methotrexate, demonstrating cytocidal activity against lung, ovary, breast, and colon cancer cell lines (3, 4). Piritrexim manifested modest activity in the National Cancer Institute tumor panel against P388 leukemia, Sarcoma 180, Ehrlich ascites, and Walker 256 carcinoma (2). Preclinical toxicology studies of piritrexim performed in both rats and dogs demonstrated that enteritis and myelosuppression were the major toxicities.

In this report we present the results of the first phase I trial and pharmacokinetic study of piritrexim performed in pediatric patients with refractory cancer. Piritrexim was administered p.o. every 12 h for 5 consecutive days. This schedule was chosen based both on the schedule dependence of piritrexim demonstrated in preclinical trials (2), and on the results of adult phase I trials (5). The aim of this study was to identify the optimal dose for phase II trials, to describe the pharmacokinetics of piritrexim in children, and to attempt to define the relationship between the pharmacokinetic parameters and toxicity. In addition, we investigated a limited sampling strategy for piritrexim that would allow for reliable estimates of the AUC,[2] based on plasma drug concentrations obtained at a limited number of time points.

## MATERIALS AND METHODS

**Patient Eligibility.** Pediatric patients between the ages of 5 and 21 years with histologically confirmed cancer refractory to conventional therapy were eligible for this trial. Patients must have recovered from the toxic effects of prior therapy before receiving piritrexim. All patients had adequate hepatic and renal function as defined by a serum bilirubin less than 1.5 mg/dl, serum transaminases less than 2 times normal, and a creatinine less than 1.5 times normal for age. Patients with solid tumors (without bone marrow involvement on biopsy) were required to have a granulocyte count greater than 1500/μl and a platelet count greater than 100,000/μl.

Prior to entry on study informed consent was obtained from the patient or his/her parent in accordance with individual institutional policies.

**Study Design.** The primary objective of the phase I trial was to define the toxicities and determine the maximally tolerated dose of piritrexim in children administered a p.o. dose every 12 h for 5 consecutive days. Courses were repeated every 21 days. A minimum of three patients evaluable for toxicity were treated at each dose level, with at least two having adequate bone marrow function to evaluate hematological toxicity. The starting dose for this study was 290 mg/m²/day for 5 days, which was less than 80% of the adult MTD on the same schedule. The dose was then lowered to 200 and 140 mg/m²/day because of DLTs observed at 290- and 200-mg/m²/day dose levels.

Patients were monitored with complete blood counts, electrolytes, creatinine, calcium, phosphorus, uric acid, liver function tests, and urinalysis weekly, and were also closely followed for clinical signs of toxicity. In patients with measurable disease, other laboratory or radiological examinations pertinent to tumor response were obtained prior to each cycle.

Patients were removed from study if they experienced unacceptable toxicity (grade 3 or 4 according to NCI-CTEP guidelines) or if objective disease progression was noted after one or more courses of piritrexim. This phase I trial defined the recommended phase II dose as the highest

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[2] The abbreviations used are: AUC, area under the plasma concentration-time curve; MTD, maximum tolerated dose; DLT, dose limiting toxicity.

dose at which at least 4 of 6 patients treated did not exhibit dose limiting toxicity.

**Drug Formulation and Administration.** Piritrexim (isethionate salt) was supplied by Burroughs Wellcome Co. (Research Triangle Park, NC) as capsules of 25- and 100-mg potency. The dose was administered every 12 h (at least 1 hour prior to or at least 2 h after a meal) for 5 consecutive days. The i.v. preparation used for pharmacokinetic studies in two patients was supplied as the isethionate salt in a solution of 8 mg/ml piritrexim dissolved in propylene glycol/water for injection (1:1, v/v). Prior to use, the piritrexim isethionate injection was diluted in sterile 5% dextrose in water to a final concentration not in excess of 0.36 mg/ml and was infused through a central venous catheter over 4 h.

**Pharmacokinetic Studies.** Seventeen patients were studied on the third, fourth, or fifth day of the first cycle of piritrexim, when steady state conditions presumably existed. Blood samples were obtained prior to a p.o. dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h after the dose. The blood samples were collected in heparinized tubes and placed on ice until the plasma was separated by centrifugation. Plasma samples were stored frozen at −20°C until assayed.

Two patients, one treated at the 140-mg/m$^2$/day dose level and another treated at the 200-mg/m$^2$/day dose level, received an i.v. 4-h infusion of piritrexim on their second or third course of therapy in place of the first p.o. dose. Pharmacokinetic data were derived from plasma samples obtained prior to the dose, and at 1, 2, 4, 4.25, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, and 24 h following the start of the infusion. Bioavailability was determined by obtaining the ratio of the AUC following the p.o. dose to the AUC following the i.v. dose ($AUC^{p.o.}/AUC^{i.v.}$).

Prior to assay, piritrexim was extracted from plasma by a previously described method (6), in order to separate the drug from metabolites which interfere with the assay. Briefly, 250 $\mu$l of plasma are alkalinized to a pH > 10 with 50 $\mu$l of 4 N sodium hydroxide, and extracted with 5.0 ml of methylene chloride by shaking for 15 min. Following centrifugation, the aqueous phase containing the more polar metabolites was discarded, and the methylene chloride was evaporated to dryness under nitrogen at 55°C. Parent drug was solubilized in 250 $\mu$l of a 1% bovine albumin solution by heating to 55°C for 30 min. Recovery was greater than 90%. Piritrexim from the extract was assayed using the dihydrofolate reductase inhibition assay (7), which has a lower limit of detectability for piritrexim of 0.05 $\mu$M. The coefficient of variation on a single day was <2%, and day to day it was 11%.

Pharmacokinetic parameters were determined by model-independent methods. Area under the plasma concentration-time curve from time 0 to 12 h was derived by the trapezoidal method (8). The AUC from 0 to 12 h measured at steady state is equivalent to the AUC extrapolated to infinity following a single dose (9). In the two patients studied following i.v. piritrexim, total clearance ($Cl^{total}$) was calculated by dividing the i.v. dose by the AUC, and the volume of distribution at steady state ($Vd_{ss}$) was calculated from the area under the moment curve (10). The terminal half-life ($t_{½}$) was determined by regression analysis.

**Limited Sampling Analysis.** Several recent studies have demonstrated that a limited sampling strategy, in which reliable estimates of the AUC are based on plasma drug concentrations obtained at a minimal number (2 or 3) of time points, may be useful in predicting pharmacodynamic responses (11–14). In the case of a p.o. administered drug, reliable estimates of AUC might also be used to assess bioavailability. The feasibility of a limited sampling strategy for p.o. piritrexim was tested by using stepwise forward multiple regression analysis as described by Ratain (11). The analysis was performed on plasma drug concentrations at each time point *versus* AUC in order to define the time points which provide the most predictive information about the AUC (11). The *F* test was used to select the optimal strategy. In addition, separate univariate analyses were performed for the concentrations at each time point *versus* the AUC.

**Pharmacodynamic-Pharmacokinetic Correlation.** The 12-h plasma concentration of piritrexim in the patients with dose limiting toxicity was compared to the concentration in patients without dose limiting toxicity, using the nonparametric Mann-Whitney *U* test (16).

Table 1 *Patient characteristics*

| | |
|---|---|
| No. of evaluable patients | 18 |
| No. of courses | 32 |
| Male/Female | 14/4 |
| Age (yr) | |
| Median | 13 |
| Range | 8–19 |
| No. of patients with prior therapy | |
| Chemotherapy alone | 2 |
| Chemotherapy + radiotherapy | 16 |
| Diagnoses | |
| Ewing's/peripheral neuroepithelioma | 11 |
| Acute lymphoblastic leukemia | 3 |
| Synovial cell sarcoma | 1 |
| Rhabdomyosarcoma | 1 |
| Clear cell sarcoma | 1 |
| Poorly differentiated yolk sac tumor | 1 |

## RESULTS

**Phase I Trial.** A total of 19 patients were entered on study. Eighteen were evaluable for toxicity, including 14 who were evaluable for hematological toxicity. One patient who developed dose limiting mucositis was judged inevaluable for toxicity because concomitant radiation therapy to the oral mucosa had been administered.

The characteristics of the evaluable patients are listed in Table 1. All had been heavily pretreated with multiple chemotherapeutic regimens and, in the vast majority of cases, radiation therapy.

Both hematological (Table 2) and nonhematological toxicities were dose limiting on this trial. Nadir granulocyte and platelet counts occurred at a median of 8 and 12 days, respectively, with recovery by a median of 13 and 15 days. Mucositis was dose limiting[3] in two patients with acute lymphoblastic leukemia treated with 290 mg/m$^2$/day. In patients with solid tumors mucositis was not severe.

Non-dose limiting toxicities included transient elevation of serum transaminases in 2 patients treated at the 290-mg/m$^2$/day dose level and in 3 patients at the 200-mg/m$^2$/day dose level (maximum serum glutamine oxaloacetic transaminase, 190 units/liter, serum glutamic pyruvic transaminase 765 units/liter). Mild nausea occurred in 2 patients treated with 290 mg/m$^2$/day and in 1 patient treated with 140 mg/m$^2$/day. A nondesquamating erythematous rash was observed in one patient at each dose level. One patient treated with 290 mg/m$^2$/day developed a desquamating rash on the soles of his feet following each cycle of therapy.

No complete or partial responses were observed. One patient with metastatic clear cell sarcoma had a minor objective response with a >25% decrease in all of her pulmonary lesions. A second patient with rapidly progressive metastatic Ewing's sarcoma had stable disease for 6 months. One patient with acute lymphoblastic leukemia had a transient decrease in his peripheral leukemic blast cell count, from 81,900 to 700 cells/mm$^3$.

The maximally tolerated dose of piritrexim was 140 mg/m$^2$/day, administered p.o. every 12 h for 5 consecutive days. Only two of six patients treated at this dose level had dose limiting neutropenia; the remaining four patients did not experience dose limiting toxicity.

**Pharmacokinetics.** The pharmacokinetics of piritrexim was studied in 17 patients during their first cycle of piritrexim. Concentration-time curves for the three dose levels studied are shown in Fig. 1. Pharmacokinetic parameters derived from plasma concentrations are listed in Table 3. Piritrexim was rapidly absorbed with the median time to peak level occurring

[3] Grade 4, defined as oral ulcerations requiring parenteral support.

Table 2 *Hematological parameters*

| Dose (mg/m²/day) | No. of patients with DLT/ no. of patients treated | WBC Nadir | WBC No. of patients <2000/mm³ [a] | Granulocytes Nadir | Granulocytes No. of patients <1000/mm³ [a] | Platelets Nadir | Platelets No. of patients <50,000/mm³ [a] |
|---|---|---|---|---|---|---|---|
| 140 | 2/6 | 3.1 [b] (0.6–5.8) | 2 | 2.2 (0.14–4.3) | 2 | 165 (20–216) | 1 |
| 200 | 4/6 | 2.1 (1.2–5.6) | 2 | 1.1 (0.53–3.7) | 3 | 78 (24–363) | 3 |
| 290 | 6/6 [c] | 2.45 (1.1–2.5) | 2 | 1.2 (0.54–1.8) | 2 | 22.5 (17–91) | 3 |

[a] Level considered dose limiting.
[b] Data presented as median (range); number × $10^3$/mm³.
[c] Includes 2 patients with mucositis as the dose limiting toxicity.

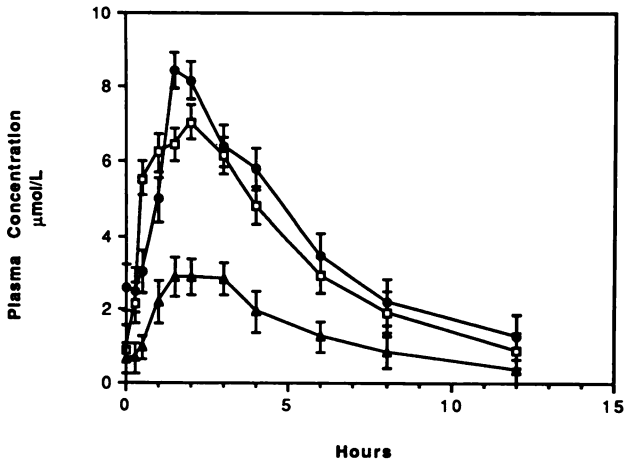


Fig. 1. Mean plasma concentrations of piritrexim in cohorts of patients treated at 140 mg/m²/day (▲, $n$ = 6); 200 mg/m²/day (□, $n$ = 5); and 290 mg/m²/day (●, $n$ = 6). *Bars*, SE.

Table 3 *Pharmacokinetics*

| Dose (mg/m²/day) | Half-life (h) | Time to peak (h) | Peak level (µM) | Trough level (µM) | AUC (µM·h) |
|---|---|---|---|---|---|
| 140 | 3.4 ± 0.27 [a] | 1.5 (1.0–4.0) [b] | 5.3 ± 0.84 [a] | 0.39 ± 0.06 [a] | 18.1 ± 2.3 [a] |
| 200 | 3.6 ± 0.35 | 1.5 (0.5–3.5) | 9.3 ± 1.7 | 0.99 ± 0.23 | 45.4 ± 8.9 |
| 290 | 4.2 ± 0.13 | 1.5 (1.5–3.0) | 10.2 ± 2.3 | 1.64 ± 0.54 | 56.9 ± 16.3 |

[a] Mean ± SE.
[b] Median (range).

1.5 h after a p.o. dose. The $t_{½}$ of piritrexim ranged from 2.4 to 4.5 h. Although there was interpatient variability, the mean AUC for patients in each dosing group correlated with the dose administered.

In the two patients treated with a single i.v. dose of piritrexim at the 140- and 200-mg/m²/day dose level, the clearance was 150 and 161 ml/min/m², and the $Vd_{ss}$ was 25.3 and 37.2 liters/m², respectively. The absolute bioavailability of p.o. piritrexim in these two patients was 35 and 93%.

**Limited Sampling Analysis.** Initially, the piritrexim concentration at each time point was correlated by linear least squares regression to the AUC. The 6-h plasma level alone strongly correlated with the AUC ($r^2$ = 0.92; $P < 0.0001$). The plasma piritrexim concentrations at all time points were then used in a stepwise forward multiple linear regression analysis. Plasma concentrations and AUC were first normalized to a dose of 140 mg/m²/day. The initial iteration chose the 6-h plasma concentration as the most informative, followed by the 3-h and then the 1.5-h concentrations. Addition of the second variable, the 3-h concentration, significantly improved the sampling strategy ($P < 0.05$) such that the correlation with AUC had an $r^2$ value of 0.98 ($P < 0.0001$). The limited sampling strategy thus chosen was defined by the following equation:

$$^{\text{Predicted}}\text{AUC} = 3.19 \cdot C_{3\,h} + 6.54 \cdot C_{6\,h} + 1.11 \cdot (\text{dose (mg/m}^2\text{/day)}/140)$$

**Pharmacodynamic-Pharmacokinetic Correlation.** The degree of toxicity in patients treated with an antimetabolite is usually related to the duration of exposure to plasma drug concentrations above a specific threshold (17). Therefore, the toxicity of piritrexim was correlated to the 12-h plasma concentration, which was the minimum plasma concentration maintained for 5 days, assuming steady state conditions. The 12-h concentration of piritrexim was significantly lower in patients without DLTs than in patients with DLTs ($P$ = 0.018; Fig. 2).

For many chemotherapeutic agents pharmacodynamic response is often best correlated with the AUC (15, 18, 19). For piritrexim, a trend toward significance ($P$ = 0.056) was found when the AUC of piritrexim in patients with DLTs (mean, 49.4 µM·h) was compared to the AUC in patients without DLTs (mean, 22.7 µM·h).

## DISCUSSION

In this pediatric phase I trial, both hematological and nonhematological dose limiting toxicities appeared to be dose related. Dose limiting toxicities were myelosuppression and mucositis. The recommended starting dose for phase II trials of p.o. piritrexim on the twice daily for 5-days schedule is 140 mg/m²/day.

Piritrexim was rapidly absorbed, with peak plasma levels occurring at a median of 1.5 h following a dose. There was, however, considerable interpatient variability in AUC at each dose level. Although this may be due to interpatient differences

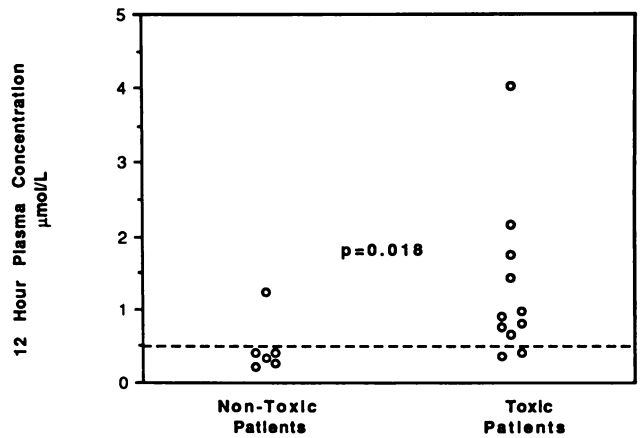


Fig. 2. Trough (12-h) plasma piritrexim concentration in patients without dose limiting toxicity compared to patients with dose limiting toxicity ($P$ = 0.018, Mann-Whitney $U$ test).

Table 4 *Pharmacokinetic comparison with adult trials*

| | Children | Adults[4] |
|---|---|---|
| Dose (mg/m²/day) | 290 | 315 |
| Half-life (h) | 4.2 ± 0.13[a] | 3.7 ± 0.55 |
| Peak level (μM) | 10.2 ± 2.3 | 12.9 ± 8.9 |
| AUC (μM·h) | 56.9 ± 16.3 | 71.9 ± 35.9 |

[a] Mean ± SE.

in drug clearance, the bioavailability data from the two patients studied (35 and 93%) suggest that it is more likely due to differences in absorption. Future trials will incorporate more patients treated with an i.v. dose to better assess bioavailability. The pharmacokinetic parameters defined in this pediatric trial are similar to those defined in adult trials (5).[4]

A significant difference in the 12-h (trough) piritrexim concentration was found when comparing patients experiencing DLTs to patients without DLTs. As seen in Fig. 2, 9 of 10 patients with 12-h plasma piritrexim concentrations >0.5 μM had dose limiting toxicity, whereas only 2 of 7 patients with trough concentrations <0.5 μM had dose limiting toxicity. This trial has thus potentially defined a plasma concentration threshold predictive of toxicity. The variable bioavailability and the definition of a toxic plasma concentration of piritrexim suggest that therapeutic drug monitoring may have a significant role in future management of patients treated with this antifolate.

In phase I clinical trials of piritrexim in adults, over 300 patients have received either the i.v. or p.o. formulation administered on several schedules (20–23). The MTD of piritrexim administered p.o. on a daily for 5-days schedule, with courses repeated every 3 weeks, was 480 mg/m²/day divided in two doses (24). Dose limiting toxicities observed were myelosuppression, rash, and mucositis.

The MTD in this pediatric trial was considerably lower than in adults. This marked difference in tolerance did not appear to be related to differences in drug disposition (Table 4). On analyzing the adult phase I data, however, patients who were heavily pretreated tolerated smaller doses of piritrexim than the untreated patients (5). This may, in part, account for the lower MTD found in this pediatric trial, since all of the patients on this trial were heavily pretreated. In future pediatric phase II trials, consideration will be given to incorporating a dose escalation for less heavily pretreated patients.

Knowledge of the AUC following p.o. administration of a drug is potentially useful, both for predicting bioavailability and pharmacodynamic response. Determination of the AUC, however, requires sampling and measurement of plasma drug concentration at multiple time points, which would be both costly and time consuming in a larger phase II trial. Limited sampling strategies are designed to accurately predict the AUC with a small number of samples. A stepwise forward multiple linear regression of individual time points *versus* AUC is one approach to developing such a strategy (11). When performed with AUC and concentration-time data from the 17 patients in this trial, the iterative analysis initially selected the 6- and then the 3-h concentrations that, when combined, correlated very well with the AUC ($r^2$ = 0.98). The relationship between toxicity and the trough plasma piritrexim concentration, and between response and either the limited sampling strategy derived AUC or the trough plasma piritrexim concentration, will be investigated further in a future trial of piritrexim.

[4] R. Blum (Burroughs Wellcome Co.), personal communication, 1989.

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