Phase I Study of Etoposide Phosphate (Etopophos) as a 30-Minute Infusion on Days 1, 3, and 5¹


ABSTRACT

Etoposide phosphate is a phosphate ester prodrug of etoposide designed to improve the pharmaceutical characteristics of the parent compound. A Phase I dose-escalating study of etoposide phosphate was conducted concurrently at two institutions to determine its toxicity, pharmacokinetics, and maximum tolerated dose. Etoposide phosphate was administered i.v. for 30 min on days 1, 3, and 5 every 21 days or on recovery from toxicity. Cohorts of at least three patients received etoposide phosphate at dose levels from 50 mg/m² to 150 mg/m² expressed as molar equivalents of etoposide. Blood and urine samples were obtained from all patients during the first cycle of treatment and the concentrations of etoposide phosphate and etoposide were measured. Thirty-nine patients with documented cancers received a total of 75 cycles of etoposide phosphate. The dose-limiting toxicity was myelosuppression which occurred at the 150-mg/m² etoposide equivalent dose. Etoposide phosphate was rapidly and extensively converted to etoposide. No measurable etoposide phosphate was detectable in the plasma by 15–60 min after the end of the infusion. The mean half-life of etoposide at the different dose levels ranged from 5.5 to 9.3 h. The pharmacokinetics of etoposide, generated from etoposide phosphate, was linear over the dose range studied and was comparable to results reported in the literature for i.v. etoposide. In summary, i.v. etoposide phosphate is rapidly and extensively converted to etoposide. The maximum tolerated dose of etoposide phosphate when given on days 1, 3, and 5 is 150 mg/m²/day. The dose-limiting toxicity is myelosuppression. The maximum tolerated dose and adverse event profile are consistent with those of etoposide.

INTRODUCTION

Etoposide, a semisynthetic podophyllotoxin derivative, entered clinical trials in 1972. It has been shown to be active as a single agent as well as an important component in combination chemotherapy. Etoposide has been used effectively in the treatment of small cell lung cancer, germ cell tumors, Hodgkin’s disease, non-Hodgkin’s lymphomas, acute leukemia, and Kaposi’s sarcoma (1). Because of its poor solubility in water, etoposide is formulated with Tween 80, polyethylene glycol, and alcohol. It is usually diluted to a final concentration of 0.2–0.4 mg/ml and administered over 30–60 min. The dose-limiting toxicity of etoposide at standard doses is myelosuppression. Other toxicities are generally modest but hypotension and metabolic acidosis occur occasionally and are thought to result from the formulation of etoposide, and not the drug itself (2, 3).

Etoposide phosphate is a derivative of etoposide designed to improve the pharmaceutical characteristics of the parent compound. Its greater polarity results in water solubility up to 20 mg/ml, so that its formulation does not require excipients that may contribute to toxicity.² Etoposide phosphate is rapidly converted to etoposide in vivo, presumably by endogenous phosphatases, and is expected to have the same therapeutic characteristics and safety profile as the parent compound (4). A Phase I trial of etoposide phosphate was conducted simultaneously at the Regional Oncology Center in Syracuse, NY, and the Fox Chase Cancer Center in Philadelphia, PA. The purpose of this study was to determine the maximum tolerated dose and pharmacokinetics of etoposide phosphate when given as a 30-min infusion on days 1, 3, and 5 every 21 days. We show that on clinical and pharmacological grounds, etoposide phosphate is expected to have a safety profile similar to that of etoposide.

MATERIALS AND METHODS

The patients eligible for this trial all had histologically proven cancer that had failed conventional therapy, or had a tumor responsive to etoposide. Age ranged from 18 to 75 years. An Eastern Cooperative Oncology Group performance status of 0–1 as well as a minimum of 12 weeks life expectancy were required. Patients had to have a WBC >4000/mm³, platelets >100,000 mm³, and adequate liver and kidney function (bilirubin, <2.0 mg/dl; serum creatinine, <1.5 mg/dl). Patients who had received cytotoxic drugs or radiotherapy within the previous 4 weeks or nitrosoureas within the previous 8 weeks were not eligible to participate. All patients gave written informed consent.

Pretreatment evaluation included a complete history and physical examination, laboratory evaluation with a complete

¹ This work was supported in part by a grant from Bristol-Myers Squibb.
² To whom requests for reprints should be addressed, at Regional Oncology Center, 750 East Adams Street, Syracuse, NY 13210.
blood count, prothrombin time and partial thromboplastin time, serum electrolytes, blood urea nitrogen and creatinine, serum electrolytes, aspartate transaminase, alanine transaminase, alkaline phosphatase, bilirubin, total protein, albumin, urinalysis, electrocardiogram, and chest X-ray. These indices were repeated before each cycle of therapy and after termination of therapy. Other imaging procedures were done as indicated for patients with evaluable disease. A complete blood count with differential and platelets, transaminases, alkaline phosphatase, bilirubin, total protein, and albumin were repeated twice weekly after the first course of therapy and weekly in subsequent courses. Blood urea nitrogen and creatinine were measured every other week. Tumor size was assessed before each course of chemotherapy and at the end of treatment. Clinical toxicity was evaluated at each patient visit.

Patients with complete disappearance of all measurable tumors and of all signs and symptoms of disease for at least 4 weeks were considered to have complete responses. Patients with a decrease of at least 50% in the sum of the products of the two largest perpendicular diameters of all measurable tumors, maintained for at least 4 weeks, and without new lesions during this interval were considered to have a partial response.

**Dose Levels and Administration.** Etoposide phosphate used for injection (Bristol-Myers Squibb Co., Princeton, NJ) in this study was a white to off-white lyophilized powder containing 113.6 mg etoposide phosphate. The vials were reconstituted with 10 ml sterile normal saline or 5% dextrose solution to produce a concentration equivalent to 10 mg etoposide/ml. After reconstitution, the appropriate, accurately measured volume of drug solution was withdrawn and further diluted to 120 ml to prepare the dosing solution. A 100-ml aliquot of the dosing solution was administered to the patients by constant rate infusion over 30 min using a calibrated infusion pump. The excess volume was used to prime the infusion tubing and pump.

The starting dose of etoposide phosphate was the molar equivalent of 50 mg/m² etoposide, administered on days 1, 3, and 5 of a 21-day cycle. Etoposide phosphate (produrg) dose is reported by dose level of the molar equivalent etoposide (active drug) dose. For example, a 57-mg/m² dose etoposide phosphate is equivalent to a 50-mg/m² dose etoposide. Doses were escalated by the etoposide equivalent of 25 mg/m² until the maximum tolerated dose was reached. At least three patients were entered at each dose level, and the dose was increased if no unacceptable toxicity was observed. Toxicities were reported using the WHO grading system. Unacceptable toxicity was defined as WHO grade III or greater hematological toxicity, nausea, or vomiting, or WHO grade II or greater nonhematological toxicity (other than alopecia). If any of the first three patients at a given dose level developed unacceptable toxicity, one to three additional patients were entered at that dose level. The maximum tolerated dose was defined as the highest dose that did not produce unacceptable toxicity in more than one third of the patients. Therapy was repeated every 3 weeks until disease progression or patient refusal. Individuals could have their dose escalated if they had no dose-limiting toxicity and at least one other patient had been treated at the higher dose with no dose-limiting toxicity. Colony-stimulating factors were not given.

**Pharmacokinetic Sample Collection and Handling.** Blood samples (7 ml) for pharmacokinetic analyses were collected at predose and over 32 h following day 1 treatment. The samples were collected in Becton-Dickinson Vacutainer tubes containing K₃EDTA; etoposide phosphate has been shown to be stable for up to 2 h in human blood collected in tubes containing EDTA and stored at 4°C (4). The sample collection times were 0 (predose), 10, 20, 30 (end of infusion), and 45 min and 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, and 32 h. Samples were obtained through an i.v. catheter placed in the forearm contralateral to that used for drug administration. Following blood collection, the tubes were gently inverted a few times to ensure thorough mixing and immediately placed on iced ice. The samples were centrifuged within 30 min of collection at 1000 × g for 10 min at 4°C. Plasma was separated and transferred into labeled screw-capped tubes and stored frozen at −20°C until analyzed for etoposide phosphate and etoposide.

A spot urine sample was collected predose, and total urine output was collected at the intervals 0–12, 12–24, and 24–32 h. The total volume of urine collected during each interval and the pH were recorded. A 20-ml aliquot of each sample was transferred into a labeled polyethylene bottle and stored at −20°C until analyzed for etoposide.

**Assay of Study Samples.** The concentrations of etoposide phosphate and etoposide in plasma and etoposide in urine were determined using validated HPLC assay methods (4). Briefly, the assay of etoposide phosphate involved solid-phase extraction of 0.5 ml plasma, followed by reverse-phase HPLC with fluorescence detection. The standard curves were linear over a range of 0.01–1 µg/ml, with a coefficient of determination \( r^2 \) ≥0.994. Plasma QC samples containing etoposide phosphate were prepared, stored, and assayed with the study samples. The predicted concentrations of the QC samples were within 11% of their nominal values, and between- and within-day assay variabilities were less than 12%. The assay of etoposide in plasma involved the addition of internal standard, 17 β-estradiol (Mead Johnson Co., Evansville, IN) to 0.5 ml plasma, followed by liquid extraction of plasma with methylene chloride, and reverse-phase HPLC with electrochemical detection. The standard curves were linear over the range of 0.1–10 µg/ml, with \( r^2 \) ≥0.992. Plasma QC samples containing etoposide were prepared, stored, and assayed with the study samples. The predicted concentrations of the QC samples were within 13% of their nominal values. The between-day and within-day assay variabilities were less than 11%. For the quantitation of etoposide in urine, the assay method was similar to the procedure previously described for plasma with the following exceptions: isolation of the analyte from urine involved solid-phase extraction using a C-18 Bond Elut column, and the analytes were eluted with chloroform. The stationary phase, mobile
phase, and mode of detection were the same as outlined for etoposide in plasma. The standard curves were linear over the range of 0.1–10 μg/ml, with $r^2 \geq 0.993$. The predicted concentrations of the QC samples were within 7% of their nominal values. The between-day and within-day assay variabilities were less than 6%. All the standard curves and QC data indicated that the assays had good precision and accuracy, and that the analytes were stable under storage and assay conditions.

**Pharmacokinetic Data Analysis.** Plasma concentration versus time data of etoposide phosphate and etoposide were evaluated using a noncompartmental method (5). AUC$_{inf}$ and AUMC were calculated using the trapezoidal and log-trapezoidal summations, with extrapolation to infinity. The terminal log-linear phase of the plasma concentration-time curve was identified by least squares linear regression analysis of at least three data points which yielded a minimum mean square error. The absolute value of the slope of this log-linear phase was the terminal elimination rate constant, $K$. The terminal elimination $t_{1/2}$ was determined from the relationship: $t_{1/2} = 0.693/K$. The $C_{max}$, time to achieve $C_{max}$, $T_{max}$, and the percentage of UR were observed values. The percentage of UR for etoposide was based on dose corrected for molecular weight difference between etoposide phosphate and etoposide. MRT for etoposide was determined from the equation: $MRT = \frac{AUMC}{AUC_{inf}} - (T*^2/2)$, where $T*$ is the infusion time. Total systemic CL was calculated from the relationship: $CL = \frac{(Dose) \cdot AUC_{inf}}{CL_{R}}$, calculated from the formula $CL_{R} = \frac{UR(O-t)}{AUC(O-t)}$, where UR is the cumulative amount of etoposide excreted in urine and $r$ is 32 h. CL$_{SS}$ was determined from the formula: $CL_{SS} = CL \cdot MRT$. Since the $F$ is not known, CL and $V_{SS}$ for etoposide are apparent systemic CL/F and apparent $V_{SS}/F$, respectively. It was not possible to calculate AUC$_{inf}$ for etoposide phosphate, due to its rapid elimination, therefore, $AUC(O-T)$, where $T$, the last measurable concentration time point, was calculated using the trapezoidal rule.

**Statistical Methods.** Linear regression analyses were performed to assess the relationship between $C_{max}$ and $AUC_{inf}$ of etoposide and the administered dose of etoposide phosphate. A test for nonlinearity was performed using the lack-of-fit $F$ statistic (6). In the absence of significant nonlinearity, a test of the significance of the estimated slope parameter was used to evaluate dose linearity; the significance of the estimated intercept parameter was used to assess dose proportionality. Residual plots were used to evaluate the appropriateness of a weighted regression (weights of reciprocal dose). The other pharmacokinetic parameters (MRT, $t_{1/2}$, CL/F, $V_{SS}/F$, $CL_{R}$, and percentage of UR) were evaluated for dose dependency using a one-way ANOVA model. The Tukey-Kramer (7) multiple comparison procedure was used for pairwise comparisons among dose levels if the overall $F$ statistic was significant. Levene’s test (8) was used to evaluate the assumption of homogeneity of variance. Simple correlations (Pearson) of etoposide AUC$_{inf}$ and hematological toxicity (nadir blood counts) were calculated and tested for significance. All analyses were performed using SAS version 5.18 (9). With the exception of Levene’s test, which was evaluated at the 0.1% significance level, all hypotheses were tested at the 5% significance level.

**RESULTS**

Thirty-nine patients received a total of 75 cycles of etoposide phosphate. The number of courses per patient ranged from one to seven. Thirty-one patients had received prior chemotherapy, while four patients had no prior chemotherapy or radiation therapy. Median age of the patients was 61.6 (range, 34–78) years. The majority of patients had non-small cell lung cancer or colorectal cancer (Table 1).

**Hematologic Toxicity.** The principal and dose-limiting toxicity of etoposide phosphate was hematological (Table 2). Both leukopenia and neutropenia were dose related, and dose-limiting toxicity was reached at 150 mg/m$^2$. As with etoposide, thrombocytopenia was less frequent, but was manifest at the highest doses. At 150 mg/m$^2$, grade III anemia was observed in one patient. At the maximum tolerated dose of 150 mg/m$^2$, nadir leukocyte count occurred at a median of 15 (range, 3–22) days after treatment, with a similar result for neutrophil count. The duration of absolute neutropenia was relatively brief with a mean of 3–4 days, although in the patient treated at 175 mg/m$^2$ it lasted for 9 days.

**Nonhematologic Toxicity.** Nonhematologic toxicity attributable to etoposide phosphate was generally mild. Grade III nausea/vomiting was seen in 3 patients, though 5 patients had grade II nausea/vomiting. Mucositis was seen in six patients, but only one had severe (grade III) toxicity. Alopecia was observed in 15 patients, but was severe in only 3. A possible hypersensitivity reaction was seen in the patient treated at 175 mg/m$^2$. It began 2.5 h after completion of drug administration on day 1, and again 3 h after drug adminis-
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The patient was premedicated with diphenhydramine, hydrocortisone, and acetaminophen for all further treatments with etoposide phosphate. No other serious toxicity attributable to etoposide phosphate occurred.

**Pharmacokinetics.** A pharmacokinetic evaluation was performed on samples from all patients. The plasma profiles of etoposide phosphate and etoposide at the various dose levels are summarized in Table 5. Linear regression analysis demonstrated a dose proportional increase in the Cmax (Cmax = 0.73 + 0.26*Dose, r² = 0.78) and AUCinf (AUCinf = 16.1 + 0.97*Dose, r² = 0.60) of etoposide (Fig. 2). Mean ratios of area under the curve of intact etoposide phosphate to that of etoposide were 1%. The remaining pharmacokinetic parameters of etoposide (MRT, t1/2, CL/F, VSS/F, CLR, and percentage of UR) were all invariant with dose. The mean percentage dose of etoposide phosphate excreted in urine as etoposide ranged from 27.8 to 43.1%.

Exposure of patients to etoposide following etoposide phosphate administration was correlated with the degree of bone marrow suppression. Simple correlation (Pearson) analysis showed significant relationships between etoposide AUCinf and nadir WBCs (r² = 0.23, P < 0.01; Fig. 3), and neutrophils (r² = 0.30, P < 0.01). However, the correlation coefficients were weak, suggesting that factors other than etoposide AUCinf are necessary to explain the observed hematological toxicity.

**Response.** There was no evidence of antitumor activity in this Phase I trial conducted in patients with demonstrated refractory carcinomas. This is not surprising given the advanced nature of the tumors treated in this trial, and that 31 of the 39 patients in this study had failed or progressed after one or more prior chemotherapy regimens.

**DISCUSSION**

Etoposide is an active drug in many cancers. Etoposide phosphate is a water-soluble derivative with greater ease of administration and possibly fewer side effects. In this Phase I study, we determined the maximum tolerated dose of etoposide phosphate to be 150 mg/m²/day (molar equivalent to etoposide) when given i.v. over 30 min on a day 1, 3, and 5 schedule. This schedule was chosen because etoposide has been used in similar

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**Table 2** Number of patients with worst WHO grade of hematological toxicity for all patients during first course of etoposide phosphate treatment

<table>
<thead>
<tr>
<th>Leukocyte</th>
<th>Neutrophil</th>
<th>Platelets</th>
<th>Hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/m²)</td>
<td>Grade I II III IV</td>
<td>Dose (mg/m²)</td>
<td>Grade I II III IV</td>
</tr>
<tr>
<td>50</td>
<td>2 0 1 1 0</td>
<td>50</td>
<td>2 0 2 0 0</td>
</tr>
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<td>75</td>
<td>2 0 1 0 0</td>
<td>75</td>
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<td>100</td>
<td>3 0 3 4 0</td>
<td>100</td>
<td>3 0 4 3 0</td>
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<td>125</td>
<td>2 3 1 0 0</td>
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<td>2 1 3 0 0</td>
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<td>150</td>
<td>1 4 3 3 4</td>
</tr>
<tr>
<td>175</td>
<td>0 0 0 0 1</td>
<td>175</td>
<td>0 0 0 0 1</td>
</tr>
</tbody>
</table>

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**Table 3** Median of worst nadir count for each patient for all courses by starting dose level

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients</th>
<th>WBC × 10³ (mm³)</th>
<th>ANC × 10³ (mm³)</th>
<th>PLT × 10³ (mm³)</th>
<th>HGB (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>4</td>
<td>Median 3.95</td>
<td>Median 2.29</td>
<td>Median 184</td>
<td>Median 9.90</td>
</tr>
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<td></td>
<td></td>
<td>Range 1.6-6.1</td>
<td>Range 1.3-3.8</td>
<td>Range 147-469</td>
<td>Range 8.6-11.8</td>
</tr>
<tr>
<td>75</td>
<td>3</td>
<td>Median 4.10</td>
<td>Median 1.65</td>
<td>Median 187</td>
<td>Median 10.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range 2.4-4.7</td>
<td>Range 1.6-3.5</td>
<td>Range 174-272</td>
<td>Range 10.0-11.0</td>
</tr>
<tr>
<td>100</td>
<td>10</td>
<td>Median 2.25</td>
<td>Median 1.04</td>
<td>Median 219</td>
<td>Median 9.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range 1.5-5.4</td>
<td>Range 0.6-3.5</td>
<td>Range 89-390</td>
<td>Range 6.7-12.2</td>
</tr>
<tr>
<td>125</td>
<td>6</td>
<td>Median 3.45</td>
<td>Median 1.53</td>
<td>Median 225</td>
<td>Median 10.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range 2.6-5.1</td>
<td>Range 1.0-3.4</td>
<td>Range 207-384</td>
<td>Range 9.0-12.6</td>
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<tr>
<td>150</td>
<td>15</td>
<td>Median 2.30</td>
<td>Median 1.32</td>
<td>Median 144</td>
<td>Median 7.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range 0.4-3.5</td>
<td>Range 0.1-2.1</td>
<td>Range 3-367</td>
<td>Range 6.7-10.5</td>
</tr>
<tr>
<td>175</td>
<td>1</td>
<td>Median 0.8</td>
<td>Median 0.01</td>
<td>Median 10</td>
<td>Median 8.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range N/A</td>
<td>Range N/A</td>
<td>Range N/A</td>
<td>Range N/A</td>
</tr>
</tbody>
</table>

ANC, absolute neutrophil count; PLT, platelets; HGB, hemoglobin; N/A, not applicable.
Table 4  Mean (SD) pharmacokinetic parameters of etoposide phosphate during and after 30-min infusion of etoposide phosphate

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients</th>
<th>Cmax (µg/ml)</th>
<th>Tmax (h)</th>
<th>AUC(0–T) (h·µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>4</td>
<td>0.67 (0.41)</td>
<td>0.21 (0.17, 0.50)</td>
<td>0.26 (0.22)</td>
</tr>
<tr>
<td>75</td>
<td>3</td>
<td>1.77 (1.33)</td>
<td>0.33 (0.17, 0.33)</td>
<td>0.59 (0.46)</td>
</tr>
<tr>
<td>100</td>
<td>10</td>
<td>2.08 (1.62)</td>
<td>0.33 (0.17, 0.50)</td>
<td>0.75 (0.66)</td>
</tr>
<tr>
<td>125</td>
<td>6</td>
<td>3.52 (2.46)</td>
<td>0.27 (0.17, 0.50)</td>
<td>1.46 (1.21)</td>
</tr>
<tr>
<td>150</td>
<td>15*</td>
<td>1.93 (1.18)</td>
<td>0.33 (0.17, 0.50)</td>
<td>0.82 (0.65)</td>
</tr>
<tr>
<td>175</td>
<td>1</td>
<td>1.94</td>
<td>0.17</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*Median (minimum, maximum).

T = 30–73-min postinitiation of infusion.

n = 13 patients due to missed sample collections.

divided dose schedules, although the best schedule of etoposide has yet to be determined (4). At this dose, granulocytopenia was dose limiting, while anemia and thrombocytopenia were modest. Similar results are observed with etoposide (9). Significant thrombocytopenia was rare, and only 2 patients had platelet counts below 50,000. Interestingly, more severe hematological toxicity occurred at 100 mg/m² than at 125 mg/m². This probably represents variability in risk factors for toxicity, since patients at the higher doses had better performance status and less prior treatment. Therefore, in pretreated patients a maximum dose of 100 mg/m²/day on days 1, 3, and 5 may be appropriate.

The most frequent nonhematological toxicity was nausea and vomiting. Although this occurred in 24 patients, it was severe in only 5. Five patients developed mucositis, but severe mucositis was seen in only one patient. One possible hypersensitivity reaction was observed. No other significant toxicity, WHO grade ≥2 was seen. Although the drug was infused over only 30 min, none of the patients developed hypotension. This has also been true when the drug was infused over 5 min (4). A hypersensitivity reaction was seen in one patient. Therefore, it is possible that such reactions are not just from the excipient used with etoposide, but may also be cause by the etoposide itself. The limited data do not allow a definite conclusion. All toxicities were consistent with those reported for etoposide and no toxicity unique to etoposide phosphate was noted.

Following i.v. administration, etoposide phosphate was rapidly cleaved in vivo, generating plasma levels of etoposide. The mean ratios of area under the curve of intact etoposide phosphate to that of etoposide, which were ≤1% at all dose levels, indicate that the main circulating species after i.v. infusion of etoposide phosphate was etoposide. The dose proportional increases observed for the Cmax and AUCinf of etoposide, and the fact that Tmax corresponded to the end of infusion, show that the rate and extent of conversion of etoposide phosphate to etoposide did not change as the dose of etoposide phosphate was increased. The other pharmacokinetic parameters of etoposide (MRT, t½, CL/F, VSS/F, CLR, and percentage of UR), which were dose independent support the conclusion that the pharmacokinetics of etoposide was linear following dosing with etoposide phosphate. The pharmacokinetic results indicate that the conversion of etoposide phosphate to etoposide is not saturated
over the dose range of 50–175 mg/m². In addition, the pharmacokinetic parameters of etoposide are comparable to results obtained with i.v. etoposide (10–15).

There are several potential advantages for using etoposide phosphate. Etoposide is active at high doses and is often used in bone marrow transplant protocols (16, 17). However, due to its lack of solubility and potential to cause hypotension, large fluid volumes and long infusion times are necessary. These difficulties may be circumvented with etoposide phosphate. Another use of etoposide phosphate may be prolonged continuous infusion via implantable infusion pump, due to the small volume in which etoposide phosphate may be diluted. Oral etoposide phosphate may have improved and more predictable bioavailability compared with etoposide. Appropriate studies are presently underway.

This study shows that etoposide phosphate is a prodrug which is rapidly and completely converted to etoposide in vivo, and that etoposide generated from etoposide phosphate exhibits linear pharmacokinetics over the dose range studied. The toxic effects of etoposide phosphate are comparable to those observed with etoposide and no unusual side effects are observed. Eto-

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**Figure 2** The relationship between mean ± SD etoposide $C_{\text{max}}$ (A) and $AUC_{\text{inf}}$ (B) and the dose of etoposide phosphate administered. Doses are expressed as etoposide equivalents.
Etoposide phosphate may offer significant advantages over etoposide which include possibility of more rapid infusion without hypotension, a smaller obligate fluid load, and avoidance of metabolic acidosis.

REFERENCES


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