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Phase I and pharmacokinetic study of etoposide phosphate

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Etoposide phosphate (EP) is a water-soluble derivative of etoposide (VP-16), a semisynthetic podophyllotoxin which is useful in the treatment of a wide variety of hematological malignancies and solid tumors. Because etoposide is poorly water soluble, it must be dissolved in a variety of organic solvents and given in relatively large volumes of saline. EP is rapidly converted to the parent drug *in vivo* and has been shown to be active in animal studies. We performed a phase I pharmacokinetic study in 27 patients. Three patients each received an etoposide-equivalent dose of 50 or 75 mg/m^2 each day by i.v. bolus (5 min) daily for 5 days and 21 patients received a dose equivalent to 100 mg/m^2 of etoposide each day for 5 days. Non-compartmental pharmacokinetic data were obtained for 22 of the patients. As with previous studies, EP behaves as a prodrug of etoposide. The C_{max} (25.3–42.5 μg/ml) increased linearly, while AUC_{inf} (75.8–156 h μg/ml) of etoposide increased proportionately with dose (50–100 mg/m^2 of etoposide equivalents). Time to achieve C_{max} corresponded to the end of the 5 min injection, indicating a rapid formation of etoposide from EP. Mean etoposide phosphate/etoposide C_{max} and AUC_{inf} ratios were 0.08 or less and 0.003, respectively, indicating that the major circulating moiety in plasma was etoposide. Parameters such as MRT, $T_{1/2}$, CL/F, CL^R, V_{SS}/F and %UR were dose independent. The toxicities of EP were virtually identical to those seen with etoposide, with dose-related myelosuppression, alopecia and stomatitis. Severe neutropenia was the dose-limiting toxicity. No significant problems with hypotension or allergic reactions were observed. No problems, difficulties or complications were observed as a result of bolus (5 min) administration. On the basis of phase I toxicity data, we recommend an etoposide equivalent starting dose of 100 mg/m^2/day for 5 days in previously untreated patients who have an excellent performance status. In patients who have had one or more prior chemotherapy regimens, extensive prior radiation therapy or moderately impaired performance status, we recommend an etoposide phosphate starting dose of 75 mg/m^2/day for 5 days with courses repeated at 3 week intervals.

Key words: Etoposide phosphate, pharmacokinetics, phase I.

Introduction

Etoposide, a topoisomerase II inhibitor, is a semisynthetic derivative of podophyllotoxin[1–3] which has been shown to be active in the treatment of both hematologic and solid malignancies over the past 20 years. It is frequently used in the treatment of small cell lung cancers, germ cell tumors, non-Hodgkin's lymphomas, Hodgkin's lymphomas and acute leukemias.[4–8]

Etoposide has a molecular weight of 588 Da. It is poorly water soluble, and must be solubilized in a formulation which includes polysorbate 80, polyethylene glycol, citric acid and ethanol.[9] Drug stability in solutions for i.v. administration is concentration dependent. Administration of etoposide has been associated with significant orthostatic hypotension when infused rapidly. This adverse effect is possibly related to the vehicle in which it is solubilized.[10] There is a low, but significant, rate of hypersensitivity reactions associated with etoposide, which appears to be related to the drug itself, but could also be in part associated with its solvents.[11,12]

Etoposide phosphate (EP) is a water soluble etoposide derivative which has a molecular weight of 668 Da. It is a phosphate ester of etoposide which behaves as a prodrug with minimal activity until hydrolyzed, presumably by endogenous phosphatases.[13] It is provided as a white to off-white lyophilized powder which is highly soluble in water. Once administered, EP is rapidly converted *in vivo*

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to the parent compound.[14] Because of its higher molecular weight, 113.6 mg of EP is equivalent to 100 mg of etoposide. *In vitro* studies with EP showed it to be less active, while *in vivo* studies with murine tumor models showed EP to be equivalent to etoposide in antitumor activity. The difference in findings between the two experimental systems is explained by the lack of *in vitro* conversion of EP to etoposide.[14]

The first clinical trials of EP in man were started in 1990 at the University of Newcastle.[15] In this phase I dose escalation trial, doses as high as 110 mg/m^2/day × 5 days did not cause prohibitive toxicity (all doses are given as the molar equivalent to etoposide). Pharmacokinetics were similar to those of etoposide in a crossover comparison of the two drugs.

Because EP is water soluble, we have performed a phase I trial of EP using a daily bolus in a small volume of diluent to assess the safety and feasibility of rapid administration, and to expand the existing clinical and pharmacokinetic data base.

Patients and methods

Patient population

Patients between the age of 18 and 75 were eligible for treatment if they had a histopathologically proven malignancy of any type known to be unresponsive to available therapy. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a minimum life expectancy of 2 months, and an adequate bone marrow reserve as evidenced by a minimal WBC of 4000/μl and platelet count of above 100 000/μl. Patients were excluded from this study if their serum creatinine was 1.5 mg/dl or above, their bilirubin was above 2.0 mg/dl, or if they were unable to give informed consent. Patients who had received any cytotoxic therapy or radiation therapy within 4 weeks or nitrosurea containing chemotherapy regimens within 8 weeks were not eligible to participate. Patients were also excluded if they had not fully recovered from any prior therapy or if they had an active bacterial infection.

The use of other non-cytotoxic, non-investigational medications was allowed on this study. Each individual's medication profile was fully documented.

Before beginning therapy, each patient had a full history and physical examination, assessment of tumor status by radiologic or other indicated studies, assessment of performance status, and a laboratory evaluation which included CBC, PT, PTT, urinalysis, serum electrolytes, glucose, BUN and creatinine, and liver function studies (including alkaline phosphatase, serum transaminases, bilirubin, protein and albumin). In addition, all patients had a chest X-ray and electrocardiogram prior to treatment. After the first course of treatment, each patient had a CBC twice a week and serum chemistries biweekly. All patients were assessed for toxicity weekly by a medical oncologist.

Pharmacokinetics

Blood sampling for pharmacokinetic measurements was performed on 22 patients. The samples were collected in potassium EDTA Vacutainer tubes. Blood sampling was to be performed from the arm contralateral to that used for drug administration on day 1 at 0 (predose), 5 (immediately following drug administration), 10, 20, 30 and 45 min after administration, then at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16 and 24 h after administration. Collected blood was immediately chilled. Within 30 min, the blood was centrifuged for plasma separation. Urine samples were collected, when possible, at 0–3, 3–6, 6–9, 9–12 and 12–24 h from the time of drug administration. Total urine collections were done for each time period. After volume measurement, the urine samples were mixed and aliquots were frozen at −20°C for storage and transportation. See Table 1.

Assay of study samples

The concentrations of EP and etoposide in plasma and etoposide in urine were determined using validated HPLC methods. For EP, the assay involved solid phase extraction of 0.5 ml of plasma sample with 0.5 ml of 0.2 M sodium dibasic phosphate buffer (pH 7.0) added. The resulting solution (1 ml) was transferred to a conditioned C-18 Bond Blut column (Analytichem International, Harbor City, CA) and washed with 3 ml of deionized water followed by 2 ml of chloroform. The EP was eluted with 2 ml of 1% triethylamine in methanol under vacuum. This eluate was evaporated under nitrogen gas at 30°C and then reconstituted with 200 μl acetonitrile (HPLC grade, Fisher Scientific, Fairlawn, NJ):water (10:90, v/v). A 50 μl aliquot of this solution was injected onto a Deltabond phenyl 5 micron HPLC column, 4.6 × 250 mm (Keystone Scientific, State College, PA). The mobile phase was acet-

Table 1. Number of BMY 40481 cycles administered

Dosage (etoposide molar equivalent as mg/m^2/day × 5)	Patients	Number of assessable cycles				
		1	2	3	4	7
50.0	3	0	1	1	1	0
75.0	3	0	3	0	0	0
100.0	21	11[a]	7	1	1	1

[a]One patient started, bud did not complete a second course.

onitrile:water (12:88, v/v) 0.01 M tretrmethylammonium hydroxide (Sigma, St Louis, MO) and 0.02 M ammonium phosphate, pH 3.0, at a flow rate of 1.0 ml/min. Detection of the analyte was done by fluorescence using a programmable Kratos Model 980 Detector (AB1 Analytical Kratos Division, Ramsey, NJ) with excitation at 200 nm and emission at 325 nm. The linear range of the standard curve was 10–1000 ng/ml. Quantitation was done by using the peak height response. The concentration of EP in the study sample was determined by inverse prediction from a weighted least squares regression standard curve (weighting factor = 1/concentration). Plasma quality control samples containing EP were prepared, stored and assayed with the study samples. The standard curves were linear with a coefficient of determination $r^2 \geq 0.994$. The predicted concentrations of the quality control samples were within 15% of their nominal values. The between day and within day assay variabilities were less than 16%.

Determination of the concentration of etoposide in the plasma sample used 17β-estradiol hemihydrate (Pharmaceutical Quality Control Department, Mead Johnson, Evansville, IN; lot MMKA314) as an internal standard; 50 µl of a stock 1 µg/ml 17β-estradiol solution with 200 µl of 0.2 M Na_2HPO_4 solution at pH 8.0 was added to 0.5 ml of plasma. The resulting solution was extracted with 4 ml of ethylene dichloride (High Purity Solvent, American Burdick and Jackson, Muskegon, MI), centrifuged for 5 min with the organic phase isolated, evaporated to dryness under nitrogen and reconstituted in 200 µl of acetonitrile:methanol:water (30:15:55, v/v). Then, 50 µl of the resulting solution was injected onto a Zorbax Phenyl 5 micron HPLC column, 4.6 × 250 mm (Dupont Instruments, Wilmington, DE). The mobile phase was acetonitrile:methanol:water: glacial acetic acid (30:15:54.5:0.5, v/v/v/v) containing 10 mM tetramethylammonium hydroxide pumped isocratically at a flow rate of 1 ml/min. Detection of the analytes was accomplished by means of electrochemical oxidation at +0.5 V using a ESA Model 5100A Coulochem Detector (ESA, Bedford, MA). Fresh plasma standards were prepared and analyzed during each analytical run. The linear range of the standard curve was 0.1–10 µg/ml. Quantitation was done using peak height ratios. The concentration of etoposide in the study samples was determined by inverse prediction from a weighted least squares regression standard curve (weighting factor = 1/concentration). Plasma quality control samples containing etoposide were prepared, stored and assayed with the study samples. The standard curves were linear with $r^2 \geq 0.993$. The predicted concentrations of the quality control samples were within 14% of their nominal values. The between day and within day assay variabilities were less than 9%.

The concentrations of etoposide in the urine were determined using a validated HPLC assay 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 eluted with chloroform. The stationary phase, mobile phase and mode of detection for etoposide were the same as outlined for plasma. Fresh urine standards were prepared, stored and analyzed with patient samples. The linear range of the assay was 0.1–10 µg/ml. Quantitation was done in an analogous manner to the plasma samples. The predicted concentrations of the quality control samples were within 6% of their nominal values. Between day and within day assay variabilities were less than 13%.

Pharmacokinetic analysis

Plasma concentration versus time curves obtained from the determined EP and etoposide concentrations were evaluated by a noncompartmental method.[16]

The area under the plasma concentration versus time curve extrapolated to infinity, AUC and the area under the first moment curve (AUMC) were calculated by 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 slope of this log-linear phase was the terminal elimination rate constant, K. The terminal elimination half-life was determined by the relationship: $T_{1/2} = 0.693/K$. The maximum plasma concentration C_{max}, time to achieve C_{max}, T_{max}, and the percent of dose excreted in the urine as etoposide, %UR, were the observed values from the tabulated data. For etoposide, %UR was based on dose corrected for the molecular weight difference between EP and etoposide. Mean residence time, MRT, for etoposide was determined from the equation: MRT = (AUMC/AUC_{inf}) − (T/2), where T is the infusion time. MRT for etoposide was not corrected since MRT for EP is generally less than 10% of the MRT of etoposide. Total systemic clearance, CL, was calculated from the relationship: CL = dose/AUC_{inf}. Renal clearance, CL^R, was calculated from the formula: CL^R = UR (0–t)/AUC(0–t) where t = 24 h. Steady state volume of distribution, V_{SS}, was determined from the formula V = CL × MRT_{iv}. Since the fraction of EP converting into etoposide (F) is not known, CL and V_{SS} for etoposide are the apparent systemic clearance (CL/F) and apparent volume of distribution (V_{SS}/F), respectively.

Table 2. Clinical characteristics of patients treated with EP

No. of patients	27
male/female	14/13
age (years)	
median	67
range	40–76
Prior chemotherapy regimens[a]	
median	2
range	0–6
prior XRT[b]	4
Cancer type	
ovarian	7
colon	8
gastric	1
anal squamos cell	1
non-small cell lung	2
sarcoma	3
adenocarcinoma of unknown primary origin	3
pancreas	1
bladder	1

[a]This does not include one trial of tamoxifen and one trial of medroxyprogesterone in two patients with ovarian cancer. All other regimens consist of standard cytotoxic agents, some combined with biological response modifiers.
[b]This includes one patient who received yttrium-labeled monoclonal antibody for ovarian cancer and one patient who had pelvic XRT for a prior prostrate cancer, which was in complete remission on entry into the study.

Statistical methods

Statistical relationships between the i.v. administered dose of EP and the pharmacokinetic parameters of the resulting etoposide were explored. Linear regression analyses were done to evaluate the relationship between C_{max}, AUC_{inf} and the administered dose of EP. A test for non-linearity was performed using the lack of fit F-statistic. In the absence of significant non-linearity, a test of significance of the estimated slope parameter was utilized to evaluate dose linearity. The significance of the estimated intercept parameter was utilized to assess dose proportionality. Residual plots were evaluated to determine the appropriateness of a weighted regression (weight of reciprocal dose).

The pharmacokinetic parameters, MRT, $T_{1/2}$, CL/F, V_{SS}/F, CL^R and %UR were evaluated for differences among dose levels using a one-way ANOVA model. The Tukey–Kramer multiple comparison procedure was used for pair-wise comparisons among dose levels if the overall F-statistic was significant. Levene's test was used to evaluate the assumption of homogeneity of variance. 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.

Seventeen patients, at the highest dose level, had their blood pressure measured immediately prior to, and 5–20 and 20–60 min after treatment with bolus EP in the lying, sitting and standing position. Blood pressure changes were assessed using paired t-tests for vital signs recorded immediate pretreatment and the first values available after treatment.

Results

Patient characteristics

The characteristics of patients entered into the study are summarized in Table 2. Twenty-seven patients who entered, with a median age of 67 (range 40–76) years. All but two of the patients had received prior chemotherapy which was considered specific for their disease. Of the two patients with no prior chemo-

Table 3. WHO grade of toxicity after first course of EP

	50 and 75 mg/m^2/day after 6 evaluable cycles				100 mg/m^2/day after 21 evaluable cycles			
Grade	1	2	3	4	1	2	3	4
Nausea/vomiting	4	—	—	—	7	1	—	—
Diarrhea	—	—	—	—	2	—	1[a]	—
Stomatitis	—	—	—	—	3	1	—	—
Increased LFTs (ANY)	2	—	—	—	5	1	—	—
Increased BUN/creatinine	2	—	—	—	5	2	—	—
Fatigue/weakness	4	—	—	—	11	2	1	—
Anorexia	—	—	—	—	—	—	—	—
Hair loss	3	—	—	—	2	6	2	—
Constipation	—	—	—	—	3	—	—	—
Hypotension	—	—	—	—	1	—	—	—
Neutropenia	1	1–	—	–1	—	1	3	15
Death[b]	—	—	—	—	two patients			
Anemia	1	2	1	—	4	4	5	1
Thrombocytopenia	—	—	—	—	2	2	4	1
Other								
chest pain	—	—	—	—	1	1	—	—
arrhythmia	—	—	—	—	1	1	—	—
abdominal pain/burning	—	—	—	—	1	—	—	—
edema	—	—	—	—	4	2	—	—
diaphoresis	—	—	—	—	2	—	—	—
confusion	—	—	—	—	3	—	—	—

[a]Associated with *C. difficile.*
[b]Within thirty days of treatment.

therapy, both had metastatic adenocarcinoma of unknown primary origin. All but one of the patients entered were fully evaluable. The partially evaluable patient did not complete a second chemotherapy cycle due to non-compliance. This patient was evaluated for toxicity after the first cycle of chemotherapy only.

Toxicity

EP doses equivalent to 50 and 75 mg/m^2 of etoposide were well tolerated. Fifteen courses of chemotherapy were given at a dose level of 50 or 75 mg/m^2/day for 5 days, with only minor side effects (Table 3). Severe myelosuppression was not common (e.g. ANC of below 1000/μl after one cycle of 50 mg/m^2 and ANC of below 500/μl after two cycles of 75 mg/m^2) with no episodes of neutropenic fever. A total of three transfusions were given after 15 cycles of chemotherapy: two of the transfusions were in one individual who had massive hemoptysis that was related to a pulmonary metastasis. There were no deaths within 30 days of treatment at the lower dose levels.

At the highest dose level, 100 mg/m^2/day for 5 days, the overall frequency of subjective toxicity increased significantly with stomatitis, alopecia, fatigue and nausea being more common. Five patients developed mild diarrhea lasting less than 3 days. One patient (who had a minor response to treatment after the first cycle) was taken off study after developing moderately severe neuromuscular weakness, thought to be disease related. Significant hair loss was common (i.e. grade II or III in 11 of 17 patients).

Myelosuppression was frequent and severe at the 100 mg/m^2/day × 5 dose level. During the first cycle of treatment, 15 of 21 patients developed an ANC of less than 500/μl. One of the remaining patients, who did not develop significant neutropenia, had received prophylactic granulocyte colony stimulating factor. Five of the patients, who received more than one cycle, required dose reductions by 25%. Treatment delays were common. After the first cycle (prior to any dose reductions) the median nadir WBC and ANC were 1300 and 280/μl, respectively. The median duration of the ANC nadir was 8.6 days. The median time to nadir was 15 days (range, 4–19 days).

There were three deaths within 30 days of drug administration. The first of these patients was a 39 year old male with stage i.v. pancreatic cancer who had undergone three prior chemotherapy regimens

without obtaining a clinical remission. The patient had a performance status of 1 and an elevated bilirubin at 2.1 mg/dl secondary to liver metastases. His enrollment on study was approved with his bilirubin 0.1 ng/dl above the stated exclusion criteria. He received EP at the 100 mg/m^2 dose for 5 days, then died at home on the sixth day. No infectious complications were diagnosed. The patient was not neutropenic during the time of drug administration. His death was felt to be related to progressive disease. The second patient, a 65 year old male with recurrent colon cancer, had failed 5-fluorouracil with citrovorum factor prior to entering this trial. His performance status was 1. On day 5 of his first treatment, he experienced a fall in hemoglobin from 8.5 to 6.8 and described some bleeding from the rectum. He was admitted, transfused and evaluated endoscopically without identification of a source for the bleeding. He was then discharged. On day 20 of his first cycle, he again was hospitalized with fevers and hypotension. At that time, his absolute neutrophil count was 112 and his platelet count 59 000/μl. He was diagnosed as having sepsis secondary to a pneumonia, and was treated with i.v. antibiotics and fluid resuscitation but died within 24 h of admission. The third patient was a 56 year old man with a diagnosis of adenocarcinoma of unknown primary origin and had completed his second cycle of EP before being taken off study with progressive disease on day 20. He was hospitalized for tachycardia following a paracentesis on day 20. The white count was 44 800/μl. He died 3 days later with the diagnosis of pneumonia and underlying malignancy.

Significant thrombocytopenia was less frequent, with no patients experiencing grade IV thrombocytopenia. Grade III thrombocytopenia occurred following five of the 39 cycles. The median nadir platelet count was 109 000/μl (range 15 000–339 000/μl).

At 100 mg/m^2 × 5, four patients required a transfusion. The mean fall in hemoglobin after the first cycle for all patients at this dose was 2.78 g/dl.

Pharmacokinetics

Pharmacokinetic studies were performed in 22 patients, three at the 50 mg/m^2 dose, three at the 75 mg/m^2 dose and 16 at the 100 mg/m^2 dose level. The mean concentration–time data are displayed in Figures 1 and 2 for EP and etoposide, respectively. The pharmacokinetic data are shown in Tables 4 and 5.

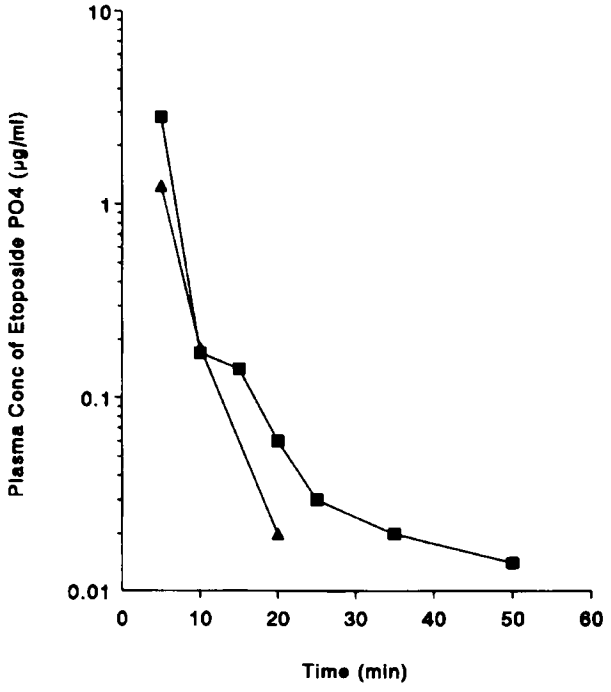

Figure 1. Mean plasma disappearance curves for EP after administration of 50 (▲) and 100 (■) mg/m^2 doses of EP.

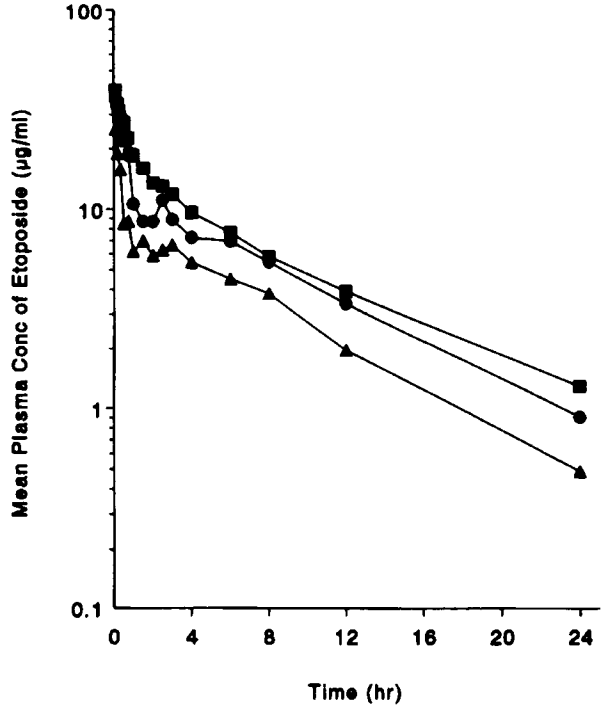

Figure 2. Plasma disappearance curves of etoposide after i.v. administration of 50 (▲), 75 (●) and 100 (■) mg/m^2 doses of etoposide equivalents.

Table 4. Mean (SD) pharmacokinetic parameters of EP after i.v. infusion of EP

Dose (mg/m^2)	C_{max} (μg/ml)	T_{max} (h)	$AUC_{(0-T)}$ (h/μg/ml)
50	1.45	0.09	0.13
($N=3$)	(0.74)	(0.01)	(0.08)
100[a]	4.02	0.09	0.45
($N=7$)	(2.28)	(0.02)	(0.31)

Pharmacokinetic parameters: C_{max} = maximum plasma concentration, T_{max} = time to achieve maximum plasma concentration, $AUC_{(0-T)}$ = area under the curve to the last non-zero time point (time + 30–50 min post-initiation of infusion).
[a]N = 7 patients due to technical problems in sample analysis or missed collection.

Table 5. Mean (SD) pharmacokinetic parameters of Etoposide after i.v. infusion of EP

Dose (mg/m^2)	C_{max} ($\mu g/m^2$)	T_{max} (h)	AUC_{inf} (h/μg/ml)	MRT (h)	$T_{1/2}$ (h)	CL/F ($ml/min/m^2$)	CL^R ($ml/min/m^2$)	V_{SS}/F (l/m^2)	%UR
50	25.25	0.09	75.78	8.00	5.60	11.08	4.80[a]	5.23	40.11[a]
($N=3$)	(0.85)	(0.02)	(8.00)	(2.04)	(1.50)	(1.22)	(0.36)	(0.83)	(0.29)
75	35.60[a]	0.08[a]	123.91	8.18	5.67	10.79	3.31	4.84	28.43
($N=3$)	(2.23)	(0.00)	(41.39)	(8.47)	(2.49)	(3.24)	(1.53)	(0.43)	(10.45)
100	42.51[b]	0.09[b]	155.97[c]	8.77[c]	6.87	11.86[c]	3.54[d]	5.74[c]	30.23[e]
($N=16$)	(4.80)	(0.01)	(58.58)	(3.31)	(2.67)	(3.50)	(1.81)	(1.28)	(12.86)

C_{max}, maximum plasma concentration; T_{max}, time to achieve maximum plasma concentration; AUC_{inf}, area under the plasma concentration versus curve from time zero to infinity; $T_{1/2}$, terminal elimination half-life; CLT/F, total body clearance divided by the fraction of EP converted to etoposide; CL^R, renal clearance; V_{SS}/F, steady state value of distribution divided by the fraction of EP converted to etoposide; EUR cumulative percent of dose excreted unchanged in the urine.
[a]$N=2$; [b]$N=10$; [c]$N=15$; [d]$N=12$; [e]$N=13$ patients due to missed or incomplete sample collection.

EP

Following i.v. administration, mean C_{max} values of EP ranged from 1.45 to 4.02 μg/ml and the median time for the occurrence of C_{max} (T_{max}) corresponded to the end of bolus injection (5 min) at both 50 and 100 mg/m^2 dose levels. Mean C_{max} of EP declined by greater than 95% within 20–25 min of the end of i.v. injection. The AUC_{inf} values ranged from 0.04 to 0.45 h/μg/ml. Comparison of EP C_{max} and AUC_{inf} values for the 50 and 100 mg/m^2 dose groups indicated an apparent dose response.

Etoposide

Mean etoposide C_{max} values ranged from 25.3 to 42.5 μg/ml for doses of EP ranging from 50 to 100 mg/m^2 of etoposide equivalents. Weighted regression analysis of C_{max} versus dose indicated a dose linear relationship ($C_{max} = 7.5 + 0.36 \times$ Dose; $R^2 = 0.92$). The mean C_{max} values of etoposide occurred at the end of bolus injection (5 min). At all doses, the levels of etoposide were markedly greater than those of EP at the end of infusion. The ratios of mean C_{max} of unchanged EP/etoposide, corrected for molecular weight differences, were 0.08 or less. These results show that etoposide was the major circulating moiety even at the end of i.v. bolus injection of EP.

Mean AUC_{inf} values of etoposide ranged from 75.8 to 156 h/μg/ml for doses of EP ranging from 50 to 100 mg/m^2 of etoposide equivalents. Weighted regression analysis of AUC_{inf} versus dose indicated a proportional relationship ($AUC_{inf} = 1.63 \times$ Dose $- 5.6$; $R^2 = -0.61$). After i.v. administration of EP, the ratios of mean AUC_{inf} of EP/etoposide, corrected for molecular weight differences, were 0.003 or less. Thus, both C_{max} and AUC_{inf} parameters indicated that etoposide was the main species in the systemic circulation.

Mean $T_{1/2}$ values of etoposide ranged from 5.60 to 6.87 h and mean MRT values ranged from 8.00 to 8.77 h. Mean values for CL/F and V_{SS}/F ranged from 10.8 to 11.9 $mg/min/m^2$ and 4.84 to 5.74 l/m^2, respectively, and mean CL^R ranged from 3.31 to 4.80 $ml/min/m^2$. The mean percent dose (expressed as etoposide equivalent) excreted in urine as unchanged etoposide ranged from 28 to 40%. MRT, $T_{1/2}$, CL/F, V_{SS}/F, CL^R and %UR were all dose independent.

Discussion

Etoposide has proven to be valuable for the treatment of a variety of neoplastic diseases, either as a single agent or in combination with other drugs. Newer applications of etoposide are being explored, including preparative regimens for bone marrow transplantation and prolonged dosing schedules for outpatients in an attempt to further enhance its efficacy. Some of the obstacles related to these applications are secondary to the lack of solubility in water.

EP is an ester of etoposide which is freely water soluble, stable and has a longer utility time after being reconstituted than its active metabolite. Once administered i.v., conversion to etoposide is rapid resulting in nearly identical pharmacokinetic and toxicity profiles to the parent compound. Thus, while this new formulation does not have enhanced cytotoxicity as compared with etoposide, it does provide new therapeutic opportunities. This would include giving higher etoposide equivalent doses without causing a metabolic acidosis or orthostatic hypotension in bone marrow preparative and other high dose regimens. More importantly, the feasibility of giving etoposide via prolonged or continuous infusions is enhanced through the use of EP. This may allow a significant advance in the treatment of recurrent and resistant tumors, as the schedule dependence of etoposide appears to be extremely important. Another significant benefit of this preparation is the flexibility of infusion times of etoposide phosphate with what may be a lower frequency of hypotension. This can allow for the substitution of etoposide in standard regimens, decreasing nursing time during administration.

The pharmacokinetic data from this study are consistent with those produced by Millward.[16] EP is nearly completely converted to etoposide within minutes, thus producing a similar C_{max}, $\beta t_{1/2}$ and AUC to those previously demonstrated for etoposide.[17] The V_{SS} and urinary excretion of etoposide after EP administration are also consistent with the etoposide data. The toxicities of the two drugs are identical, with the exception of a lack of orthostatic hypotension with EP during bolus administration. We found severe toxicity at 100 mg/m^2 on the 5 day schedule unacceptable. Included in these complications were three deaths within 30 days of treatment, one of which was treatment related. These complications were most apparent in patients who had received more than one prior chemotherapy regimen and/or radiation therapy. In light of this, we recommend a dose of etoposide phosphate equivalent to 75 mg/m^2/day of etoposide for 5 days if given as a single agent, at 3 week intervals.

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