Cancer Chemother Pharmacol (1996) 38: 378–384

ORIGINAL ARTICLE

Willi Kreis · Daniel R. Budman · Vincent Vinciguerra
Kathleen Hock · Joann Baer · Richard Ingram
Lee P. Schacter · Scott Z. Fields

Pharmacokinetic evaluation of high-dose etoposide phosphate after a 2-hour infusion in patients with solid tumors

Received: 18 July 1995/Accepted: 20 October 1995

Abstract Etoposide phosphate, a water soluble prodrug of etoposide, was evaluated at levels potentially useful in transplantation settings in patients with malignancies. For pharmacokinetic studies of etoposide phosphate in this phase I study, 21 patients with solid tumors were treated with etoposide phosphate given as etoposide equivalents of 250, 500, 750, 1000 and 1200 mg/m^2 infused over 2 h on days 1 and 2, and G-CSF 5 μg/kg per day starting on day 3 until WBC was $\geq$ 10 000/μl. Qualitative, quantitative, and pharmacokinetic analysis was performed as reported previously. Rapid conversion of etoposide phosphate into etoposide by dephosphorylation occurred at all dosage levels without indication of saturation of phosphatases. Plasma levels (C_{pmax}) and area under the curve (AUC) of etoposide phosphate and etoposide demonstrated linear dose effects. For etoposide, plasma disposition demonstrated biphasic clearance, with mean $T_{1/2}$ α of 2.09 $\pm$0.61 h, and $T_{1/2}$ β of 5.83 $\pm$ 1.71 h. An AUC as high as 1768.50 μg.h/ml was observed at a dose of 1200 mg/m^2. The total body clearance (TBC) showed an overall mean of 15.72 $\pm$ 4.25 ml/min per m^2, and mean volume of distribution (V_{Dss}) of 5.64 $\pm$ 1.06 l/m^2. The mean residual time (MRT) for etoposide was 6.24 $\pm$ 1.61 h. In urine, etoposide but not etoposide phosphate, was identified with large quantitative variations (1.83% to 33.45% of injected etoposide equivalents). These results indicate that etoposide phosphate is converted into etoposide with the linear dose-related C_{pmax} and AUCs necessary for use of this agent at the high dosage levels needed in transplantation protocols. A comparison of pharmacokinetic parameters of high- dose etoposide with the values observed in our study with etoposide phosphate revealed comparable values for the clinically important C_{pmax} and AUCs, clearance, terminal $T_{1/2}$ and MRT. In contrast to the use of etoposide, etoposide phosphate can be delivered in aqueous vehicles and therefore may offer the advantage of ease of administration.

Key words Pharmacokinetics · High-dose etoposide phosphate

Supported in part by the Don Monti Memorial Research Foundation, and the Bristol Myers Squibb Company

W. Kreis (✉) · D.R. Budman · V. Vinciguerra · K. Hock · J. Baer
Don Monti Division of Oncology, Department of Medicine, North Shore University Hospital, Cornell University Medical College, Manhasset, NY 11030, USA

R. Ingram · S.Z. Fields
State University of New York Health Science Center, Syracuse, NY 13210, USA

L.P. Schacter
Bristol-Myers Squibb Corporation, Wallingford, CT 06492, USA

Introduction

Podophyllotoxin derivatives such as etoposide have been extensively evaluated in malignant disease [1]. This agent has clinical value in the treatment of leukemia, lymphoma, germ-cell tumors, and cell lung tumors. Etoposide is also used in high-dose treatments, especially transplantation regimens [2–4]. However, at high dosages, large volumes of solvent must be administered owing to the poor solubility of etoposide in aqueous solution. Currently, etoposide is formulated in polysorbate 80, polyethylene glycol, and ethanol. This mixture of solvents is toxic to mice (Bristol Myers Squibb, unpublished data). With high-dose etoposide therapy, significant toxicities such as drug fever, hypotension, and rigors occur in more than one-third of patients [5]. High-dose treatment may require infusion rates as high as 1 l/h which can lead to fluid overload [6]. Metabolic acidosis has also been reported [5].

Etoposide phosphate (BMY-40481) is a water-soluble prodrug which does not need to be dissolved in large volumes, and is formulated without Tween 80, polyethylene glycol, or ethanol. The high solubility of

the compound allows for rapid administration of the drug and may lead to lessened acute toxicities. However, the use of this agent in a high-dose schedule in humans requires the demonstration that the prodrug is rapidly and completely metabolized to its active form, etoposide, without evidence of saturability of this step at high dose levels of etoposide phosphate. In addition, a water-soluble agent might be rapidly cleared by the kidneys, thus giving a nonlinear dose response.

In animals and humans, etoposide phosphate at conventional dosages is rapidly and extensively converted to etoposide following intravenous administration [7]. A phase I study of this agent as a bolus administration at doses up to 200 mg/m^2 on days 1, 3 and 5 in patients with solid tumors has been recently reported demonstrating classical etoposide toxicities and pharmacokinetics [8].

The present study was designed to evaluate, in a phase I study, intravenous administration of high-dose etoposide phosphate over 2 h on days 1 and 2 with the aim of eventually using this prodrug in transplantation regimens. The clinical pharmacology of this agent at doses equivalent to levels used in the transplantation setting was therefore evaluated to determine whether the prodrug would be converted to active etoposide, and to what extent, and whether dose-related increases in pharmacologic parameters could be demonstrated. Preliminary results have been reported in abstract form [9].

Materials and methods

Informed written consent following institutional guidelines, consistent with the Declaration of Helsinki, was obtained from each patient. The patients were required to have recovered from all effects of prior therapy and to meet the following criteria: CALGB performance status of 0–1, normal renal function (creatinine levels less than 1.5 mg/dl), normal hepatic function (bilirubin level less than 2.0 mg/dl), total white blood cell count equal to or greater than 4000/μl, and platelets equal to or greater than l00 000/μl. All patients were treated as outpatients.

Since the high dose range of etoposide which is tolerable in humans by prolonged infusion is already known, a conservative dose escalation scheme was employed: 250, 500, 750, 1000, and 1200 mg/m^2 of etoposide equivalents infused as etoposide phosphate. Etoposide phosphate was supplied by the Bristol Myers Squibb Company as a lyophilized powder in vials containing 113.6 mg of the drug corresponding to 100 mg of etoposide. Vials were reconstituted in 5% dextrose solution and further diluted in normal saline to a concentration of l0 mg/ml, and infused over 2 h to groups of three to six patients. We have previously shown that etoposide phosphate is stable in solution at this concentration. The drug was infused at rates ranging from 3.3 to 26.1 mg/min.

Blood samples were collected in Vacutainer tubes containing potassium EDTA as an anticoagulant at a contralateral site to the infusion at 0, 0.25, 0.5, 1, 2, 2.5, 3, 4, 6 and 24 h after the initiation of the 2-h infusion. It has been demonstrated previously [8] that, following its addition to human blood containing K_3EDTA, etoposide phosphate remains intact over 2 h at 4°C. The samples were gently mixed, placed on ice, centrifuged within 30 min of collection in a Sorvall centrifuge (DuPont Co., Wilmington, Del.) at 1200 *g* for 15 min at 4°C. Plasma was transferred to polypropylene tubes and frozen at − 80°C until analysis.

Urine samples were obtained before initiation of the infusion, and 0–3 and 3–6 h after initiation of the infusion. Aliquots of the samples were stored in polyethylene tubes at − 80°C. Stability of etoposide phosphate in urine was proven by adding standard amounts of etoposide phosphate to normal human urine followed by repeated freezing and thawing over l week or followed by storage at − 80°C for 1 week or 1 month. Extraction of etoposide phosphate and etoposide was then performed following the procedure used for plasma samples. No significantly different amounts of etoposide phosphate were found in these urine samples when compared to urine samples to which etoposide phosphate was added immediately before extraction. No etoposide was observed in the urine samples used for stability studies.

For etoposide phosphate, a solid phase extraction method was employed [8]. In brief, 0.5 ml of plasma sample was mixed with 0.5 ml of 0.2 *M* sodium phosphate, and the mixture was transferred to a C-18 Bond Elut column (Jones Chromatography, Lakewood, Colo.), washed with deionized water and eluted with 2 ml 1% triethylamine in methanol. The evaporated eluate was reconstituted in acetonitrile : water (10 : 90 v/v) and submitted to HPLC separation on a Deltabond Phenyl 5 μm column, 4.6 × 250 mm (Keystone Scientific, State College, Pa.), with an isocratic mobile phase (pH 3.0) of 0.02 M dibasic ammonium phosphate, 0.01 *M* tetramethylammonium hydroxide (Sigma Chemical Co., St. Louis, Mo.), and 12% acetonitrile (v/v). The flow rate was 1.0 ml/min, and fluorescence was measured (excitation at 200 nm and emission at 325 nm) on a Perkin-Elmer LC 240 detector (Perkin-Elmer, Norwalk, Ct.). Standard solutions from 5 to 500 ng/ml of etoposide phosphate in pooled commercial plasma (Biological Specialty Corp., Lansdale, Pa.) gave *P*-values consistently of 0.99 or more.

For the quantitation and analysis of etoposide in plasma, β-estradiol (Aldrich Chemical Co., Milwaukee, Wis.) was added to plasma as an internal standard, and the sample extracted with ethylene dichloride (American Burdick & Jackson, Baxter, McGaw Park, Ill.). Following centrifugation, evaporation of the organic phase, and resolution of the residue in acetonitrilemethanol : water (30 : 15 : 55 v/v), aliquots were separated by HPLC on a Zorbax Phenyl 5 μm 4.6 × 250 mm column (Mac-Mod Analytical, Chadds Ford, PA.), with an isocratic mobile phase of acetonitrile : methanol waterglacialacetic acid (30 : 15 : 54.5 : 0.5 v/v) containing l0 m*M* tetramethylammonium hydroxide, at a flow rate 1 ml/min. Detection was done by electrochemical oxidation at 0.5 V using an ESA Model 5100 A Coulochem Detector (Environmental Services Associates, Bedford, Mass.). Standard curves for etoposide, quality control, and variability ranges have been reported previously [8].

For etoposide in urine, the procedure was used as previously described [8]. The sensitivity for etoposide phosphate was 5.0 ng/ml, and for etoposide was 0.1 μg/ml.

Pharmacokinetic analysis of the results was performed using noncompartmental methods as described by Gibaldi and Perrier [10] and employed previously [11]. The total area under the curve ($AUC_{0-\infty}$) from the start of infusion to infinity was calculated by trapezoidal summation:

$$AUC_{0-\infty} = AUC_{(to-tlast)} + AUC_{residual}$$

where t_{last} is the last sample with + value ∞

$$AUC_{residual} = \frac{Cplast}{\lambda}(tlast)$$

where λ is the terminal rate constant evaluated by linear least square regression analysis at the terminal phase of the plasma concentration time curve after the end of the infusion. The time-points of the plasma levels (C_p) were chosen to fit by linear regression analysis. For etoposide, C_p time-points chosen for evaluation had to be at least three consecutive declining values. For etoposide $T_{1/2}$ α three consecutive time points starting with C_{pmax}, and for $T_{1/2}$ β the final

three terminal C_p values were used. Correlation coefficients (R) were calculated to evaluate the goodness of fit.

The mean residual time (MRT) for etoposide was calculated as

$$MRT = \frac{AUMC}{AUC} - \frac{T}{2}$$

where T is the infusion time and AUMC is Area under first moment curve.

$$AUMC = AUMC_{(T0-Tlast)} + \frac{Cplast(tlast)}{\lambda} + \frac{Cplast}{\lambda}$$

Total body clearance (TBC) was obtained by dividing the dose by the AUC and the volume of distribution at steady state (V_{Dss}) by multiplying MRT by TBC.

Renal clearance could not be calculated since urine was collected over only 6 h because this was an outpatient procedure.

Statistical analysis

Linear regression analysis was used to evaluate the correlation between C_{pmax} or AUC with administered dose of etoposide phosphate equivalents, and with the etoposide phosphate-derived etoposide.

Results

A total of 22 patients (9 females, 13 males) were entered. One patient (no.19) could not be analyzed because of incomplete collection of blood samples. Figure 1 illustrates the plasma decay curve for etoposide phosphate and etoposide of a representative patient infused at a dose of 1200 mg/m^2 etoposide equivalents over the time of sample collection.

Large interpatient variations were found in all pharmacokinetic parameters for etoposide phosphate. The C_{pmax} of etoposide phosphate correlated with the dose administered and reached peak levels at a dose of 1200 mg/m^2 with a mean plasma level of 7.11 $\pm$ 7.16 μg/ml (range 3.17–17.83 μg/ml). These maximum values were reached within 0.25 to 2 h, for all doses administered, and showed large interpatient variations as reflected in a relatively low R-value ($R = 0.479$, $P = 0.028$). Steady-state plasma levels were achieved only in 14 patients (67%).

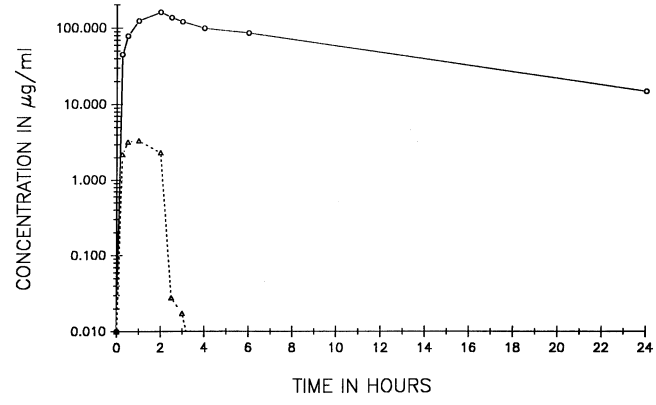

Fig. 1 Plasma decay curves from a representative patient for etoposide phosphate and etoposide over 24 h after initiation of the infusion of 1200 mg/m^2 of etoposide phosphate (○ etoposide, △ etoposide phosphate)

Table 1 Etoposide phosphate in plasma of 21 patients (values are means $\pm$ SD)

Dose mg/m^2	No.of Patients	C_{pmax} (μg/ml)	AUC (μg.h/ml)	TBC (ml/min/m^2)
250	5	0.84 $\pm$ 0.72	1.22 $\pm$ 0.95	19488 $\pm$ 33947
500	3	1.64 $\pm$ 0.37	2.64 $\pm$ 0.64	3323 $\pm$ 922
750	3	4.58 $\pm$ 6.01	7.22 $\pm$ 9.70	5420 $\pm$ 4178
1000	6	6.98 $\pm$ 7.23	7.02 $\pm$ 5.87	6326 $\pm$ 7554
1200	4	7.11 $\pm$ 7.16	6.69 $\pm$ 2.43	3332 $\pm$ 1318
Overall mean $\pm$SD				8331 $\pm$ 17006

The plasma concentration vs time AUC for etoposide phosphate was dose dependent (Table 1, Figure 2). TBC for etoposide phosphate showed large variations due to outliers, especially in the groups receiving 250 and 1000 mg/m^2 of the drug. The mean values ranged from 3300 to 6300 ml/min/m^2 for etoposide equivalent dosages above 250 mg/m^2 (Table 1). The MRT could not be evaluated for etoposide phosphate by noncompartmental analysis because of the large variance seen in the sample set determined by this study. This parameter and consequently V_{Dss} are not listed in Table 1.

In contrast, etoposide values were "well behaved" (Table 2). The C_{pmax} values of etoposide were reached

Table 2 Etoposide in plasma of 21 patients (values are means $\pm$ SD)

Dose (mg/m^2)	No of patients	C_{pmax} (μg/ml)	AUC (μg.h/ml)	$T1_{1/2}\alpha$ (h)	$T1_{1/2}\beta$ (h)	MRT (h)	V_{Dss} (l/m^2)	TBC (ml/min/m^2)	AUC^a_{EP}/ AUC_E*
250	5	33.74 $\pm$ 3.78	257.69 $\pm$ 71.62	1.56 $\pm$ 0.39	5.78 $\pm$ 1.54	5.97 $\pm$ 0.39	5.78 $\pm$ 0.39	17.74 $\pm$ 7.16	0.004
500	3	72.29 $\pm$ 8.44	561.71 $\pm$114.31	1.80 $\pm$ 0.35	5.13 $\pm$ 1.19	5.21 $\pm$ 1.36	4.65 $\pm$ 1.36	15.23 $\pm$ 2.93	0.004
750	3	87.38 $\pm$ 3.98	805.99 $\pm$ 53.45	3.03 $\pm$ 0.74	5.15 $\pm$ 1.07	5.53 $\pm$ 1.14	5.12 $\pm$ 0.79	15.55 $\pm$ 1.00	0.008
1000	6	123.35 $\pm$ 16.70	1209.40 $\pm$ 48.39	2.22 $\pm$ 0.28	7.29 $\pm$ 1.26	7.62 $\pm$ 1.40	6.28 $\pm$ 0.95	13.80 $\pm$ 0.54	0.005
1200	4	140.43 $\pm$ 16.72	1302.29 $\pm$392.78	2.07 $\pm$ 0.49	4.74 $\pm$ 2.29	5.80 $\pm$ 1.49	5.62 $\pm$ 1.69	16.56 $\pm$ 5.48	0.005
Over all means $\pm$ SD				2.09 $\pm$ 0.61	5.83 $\pm$ 1.71	6.24 $\pm$ 1.61	5.64 $\pm$ 1.06	15.72 $\pm$ 4.25	

[a]Calculated in terms of E equivalents

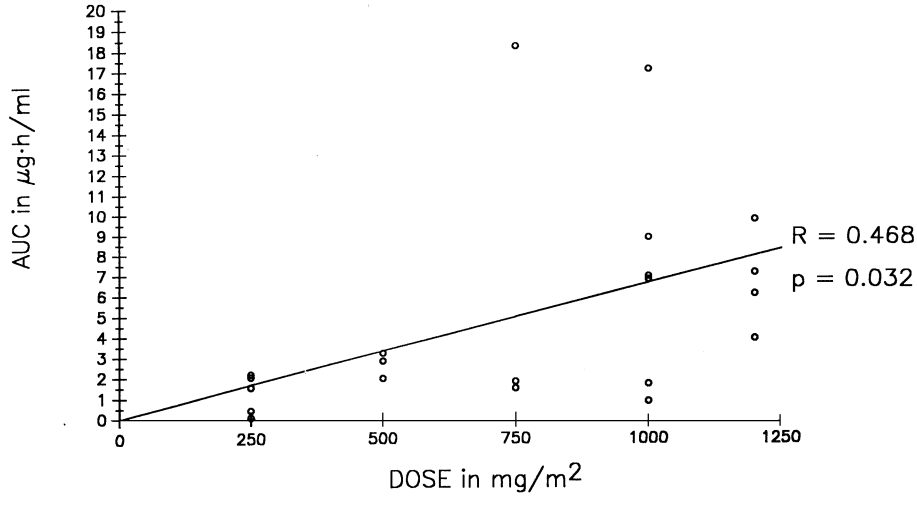

Fig. 2 Correlation between individual AUCs and dose for etoposide phosphate

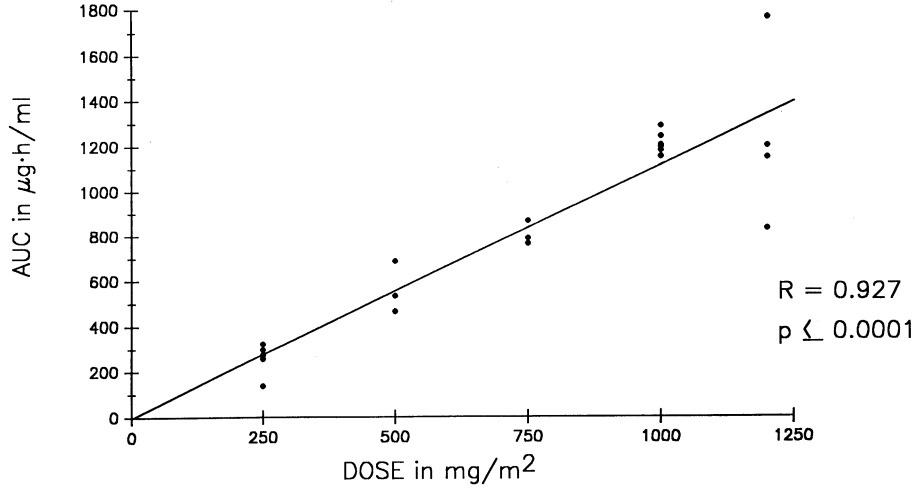

Fig. 3 Correlation between individual AUCs and dose for etoposide

consistently at 2 h, corresponding to the end of the etoposide infusion, and demonstrated less variance. This finding was reflected in the relatively small standard deviations and an R-value of 0.960 ($P = < 0.0001$) when the individual values observed at each dose were plotted against the dose of etoposide phosphate administered. Maximal etoposide C_{pmax} values were obtained at the dose of 1200 mg/m^2, with a mean at that level of 140 $\pm$ 17 µg/ml. The mean group C_{pmax} values of etoposide were consistently higher than the C_{pmax} values of etoposide phosphate by a factor of 173 to 343.

The AUC for etoposide was dose related. When the individual AUCs were plotted against the dose, an *R*-value of 0.927 with $P < 0.0001$ was obtained (Fig. 3). The mean values per group also showed good linearity. At a dose of 1200 mg/m^2 of etoposide phosphate, the mean etoposide AUC levels were 1302.20 $\pm$ 392.78 µg.h/ml (Table 2).

Plasma decay (TBC) of etoposide occurred biexponentially (Fig. 1), with a mean $T_{1/2}\,\alpha$ of 2.09 $\pm$ 0.61 h (range 1.03 to 3.82 h). For $T_{1/2}\,\beta$ the values were also dose independent and considerably longer, varying from 1.54 to 9.33 h, with an overall mean of 5.83 $\pm$ 1.71 h (Table 2). TBC was dose independent with interpatient variations ranging from 11 to 30 ml/min per m^2, but with small mean standard deviations for each dose group. The overall mean was 15.72 $\pm$ 4.25 ml/min per m^2 (Table 2). The MRT for etoposide, calculated by the noncompartmental method, revealed values ranging from 3.07 to 10.04 h. No dose dependency was observed with a mean value for all patients of 6.24 $\pm$ 1.06 h. Corresponding to the results for MRT and TBC, the V_{Dss} showed values ranging from 3.52 to 7.80 l/m^2 (mean of all individual values 5.64 $\pm$ 1.06 l/m^2).

Analysis of urine samples for etoposide phosphate and etoposide over 6 h of collection revealed varying amounts of etoposide, ranging from 1.83% to 33.45%

of the administered amounts of etoposide equivalents. There was no evidence of rapid clearance of etoposide phosphate into the urine despite the rapid infusion of this agent and its known water solubility.

Discussion

The data presented on 21 patients treated at doses from 250 to 1200 mg/m^2 demonstrated rapid dephosphorylation of the water-soluble prodrug, etoposide phosphate, to etoposide following intravenous administration over 2 h. There was no evidence of saturation of the dephosphorylation reaction at higher dosage levels. Rapid dephosphorylation of etoposide phosphate, as demonstrated in this study for high dose etoposide phosphate, is thus analogous to the observations at lower dosages of etoposide phosphate by Budman et al. [8], Sessa et al. [12] and Thompson et al. [13].

This study showed large variances in etoposide phosphate pharmacokinetic parameters which might be a consequence of genetic polymorphism of alkaline phosphatases. Two different electrophoretic patterns of human alkaline phosphatases have been reported in intestines and liver. The former is found predominantly in the serum of individuals with B and O blood groups [14]. No information exists concerning genetic differences (fast or slow phosphorylation) for alkaline phosphatase.

The rapid dephosphorylation of etoposide phosphate is characterized by a plasma disappearance $T_{1/2}$ of ≤ 5 min for the prodrug [8,12,13]. This rapid clearance may have precluded reliable and accurate evaluations of the terminal half-life of etoposide phosphate in our study. The ratios of the AUCs of etoposide phosphate to the AUCs of etoposide ranged from 0.004 to 0.008 in this study, thus comparing well with our previously reported ratios at lower dosages of ≤ 0.006 [8], and the value found by Thompson et al. of 0.009 [13]. The AUCs of etoposide phosphate in this study at a dose of 250 mg/m^2 compared to that found in our previous study [8], and those found by Thompson et al. at 200 mg/m^2 and at 100 mg/m^2 [13], are comparable: 1.22 ± 0.95, 1.87 and 0.96 ± 1.03 μg.h/ml, respectively.

A comparison of the pharmacokinetics of etoposide reported in the literature following "low-dose" (125–250 mg/m^2) administration of etoposide phosphate is outlined in Table 3. After correcting for different doses and times of administration, the C_{pmax} values are comparable. The AUCs are comparable as are the dose-independent parameters TBC and V_{Dss}. Terminal $T_{1/2}$ values were dose-independent and similar in the four studies.

Etoposide, because it is a therapeutically active agent in many malignant diseases, is commonly used in the transplant setting [15]. However, etoposide dose escalation is made difficult because of its lack of solubility. The soluble prodrug, etoposide phosphate, might thus simplify dose escalation. A comparison of pharmacokinetics of etoposide derived from etoposide phosphate with values reported in the literature for high dose etoposide, at 400 mg/m^2 to 4.8 g/m^2, infused over 30 min to 96 h, is shown in Table 4 [2, 16–21]. The dose-independent parameters reveal comparable values for TBC (range 15.5 to 24.6 ml/min per m^2), for V_D or V_{Dss} (range 4.9 to 15.0 l/m^2), and for $T_{1/2}$ terminal (4.3 to 8.7 h, with the exception of the values of Mross et al. with a value of 18.3 h). This study demonstrates that the production of etoposide from etoposide phosphate easily achieves pharmacokinetic parameters comparable to high-dose etoposide administration (Table 4). In addition, there is no evidence that the water-soluble drug is cleared by the kidney at higher dosages. The dose response of etoposide phosphate conversion into etoposide remains linear even at levels used in transplantation. Owing to the short collection time for urine in this outpatient setting, the data do not allow any conclusions as to clearance pathways except for the rapid dephosphorylation.

This study demonstrates the feasibility of the use of this agent in dosages equivalent to those used in high-dose etoposide regimens. An additional benefit may be the ability to avoid large volumes, and the toxic effects of a complex solvent formulation.

Table 3 Etoposide pharmacokinetics after i.v. administration of etoposide phosphate at comparable levels (125 to 250 mg/m^2) (*NR* not reported)

Study	Reference	EP dose (mg/m^2)	EP time of administration	C_{pmax} (μg/ml)	EP dose (mg/m^2)	Time reached (h)	AUC (μg·h/ml)	TBC (ml/min/m^2)	V_{Dss} (l/m^2)	MRT (h)	$T_{1/2}\alpha$ (h)	$T_{1/2}\beta$ (h)
Present		250–1200	2 h	33.74	250	2 hr	257.69	17.74	5.78	5.97	1.56	5.78
Budman et al.	8	50–200	Bolus	52.53	200	0.08–0.17	269.8	12.36	8.59	11.59	NR	10.02
Thompson et al.	13	50–125	30 min	26.3[a]	125	0.5	132.9	15.6	9.5	NR	NR	9.1
Sessa et al.	12	50–220	5–30 min	39.2	220	NR	151.4	24.9	10.1	NR	NR	6.0

[a] One patient only

Table 4 Pharmacokinetics of etoposide following i.v. administration of high-dose etoposide obtained from seven independent reports

Authors	Reference	Etoposide dose given (mg/m^2)	Infused over	C_{pss} or C_{pmax} (μg/ml)	AUC (μg.h/ml)	TBC (ml/min/m^2)	V_D or V_{Dss} (l/m^2)	$T_{1/2}$ terminal (h)	MRT (h)	Remarks
Brown et al.	2	1800–4800	29–69 h	37–111	55.9 ± 13.6[c]	18.9 ± 4.4	15.0 ± 5.3	8.2 ± 2.0	NR	In sequential combination with cyclophosphamide
Köhl et al.	16	700	30–40 min	156 ± 27	574.8[d]	20.4 ± 2.4	6.6 ± 1.2	4.3 ± 0.6	5.8 ± 0.8	Daily for 3 days infused after cyclophosphamide or CBDCA
Hande et al.	17	400–800	2–3 h	27–114	153 ± 974	28.0 ± 9.7	25.2 ± 10.5	8.05 ± 4.3		
Newman et al.	18	1000–3000	4 h	NR	677–2813 (linear for dose)	24.6 ± 6.8	11.8[e]	4.3 ± 1.1	8.0 ± 1.4	
Schwing Hammer et al.	19	1295–2200[a]	4 h	Total: 119.6 ± 47.3 Unbound: 22.5 ± 9.7	1273 ± 561	31.8 ± 17.7	11.5 ± 5.9	7.2 ± 3.7	NR	Evaluation of total and unbound etoposide
Relling et al.	20	780	72 h	8.1–11.4	37.1–50.5	15.5–20.0	4.9–5.2 l/m^2	8.7–11.0	NR	Multiagent chemotherapy administered in three courses
Mross et al.	21	1110–1665[a]	6 h	Diluted 143 ± 39	Diluted 1289 ± 409	Diluted 18.3 ± 5.6	Diluted 0.18 ± 0.05 l/kg	Diluted[f] 17.0 ± 12.1	Diluted 6.5 ± 2.2	Diluted: 0.5 ng/ml
				Undiluted: 156 ± 53	Undiluted 1378 ± 519	Undiluted 19.2 ± 9.0	Undiluted 0.18 ± 0.1 l/kg	Undiluted[d] 18.3 ± 131	Undiluted 6.1 ± 0.8	Undiluted: 20 mg/ml Multidrug administration
Kreis et al.	Present study	1200	2 h	140.4 ± 16.7[b]	1302.3 ±392.8	15.72 ±4.25	5.64 ± 1.06	5.83 ± 1.71	6.24 ±1.61	Daily for 2 days

[a]Conversion of mg/kg to mg/m^2 according to Freireich et al. [22]
[b]For dose of 1200 mg/m^2
[c]Insufficient information for conversion of the value indicated in $\frac{\mu g/ml \times min}{mg/m^2}$ to μg.h/ml
[d]This value kindly provided by H. Jungclas
[e]Calculated: MRT × TBC
[f]Triphasic clearance

Acknowledgement The authors thank Ms. Ruth Kaplan for secretarial help in the preparation of the manuscript.

References

1. Stahelin H, Wartburg A von (1989) From podophyllotoxin glucoside to etoposide. Progr Drug Res 33:169–266
2. Brown RA, Herzig RH, Wolff SN, Frei-Lahr D, Pineiro L, Bolwell BJ, Lowder J, Harden E, Hande K and Herzig G (1990) High dose etoposide and cyclophosphamide without bone marrow transplantation for resistant hematologic malignancy. Blood 76:473–479
3. Blume KG, Forman SJ (1992) High-dose etoposide (VP-16) containing preparatory regimens in allogenic and autologous bone marrow transplantation for hematologic malignancies. Semin Oncol 19 [suppl 13]:63–66
4. Spitzer TR, Cottler-Fox M, Torrisi J, Cahill R, Greenspan A, Lynch M and Deeg HJ (1989) Escalating doses of etoposide with cyclophosphamide and fractionated total body radiation or busulfan as conditioning for bone marrow transplantation. Bone Marrow Transplant 4:559–565
5. Chao NJ, Stein AS, Long D, Negrin R, Amylon M, Wong R, Forman S, Blume K (1993) Busulfan/etoposide — initial experience with a new preparatory regimen for autologous bone marrow transplantation in patients with acute nonlymphoblastic leukemia. Blood 81:319–323
6. Linker CA, Ries CA, Damon LE, Rugo H, Wolf J (1993) Autologous bone marrow transplantation for acute myeloid leukemia using busulfan plus etoposide as a preparative regimen. Blood 81:311–318
7. Etoposide phosphate (BMY-4048) (1991) Investigator Brochure on file with the Food and Drug Administration, Washington, DC
8. Budman DR, Igwemezie LN, Kaul S, Behr J, Lichtman S, Schulman P, Vinciguerra V, Allen S, Kolitz J, Hock K, O'Neill K, Schacter L, Barbhaiya R (1994) Phase I evaluation of a water soluble etoposide prodrug, etoposide phosphate, given as a 5-minute infusion on days 1,3 and 5 in patients with solid tumors. J Clin Oncol 12:1902–1909
9. Kreis W, Budman DR, Fields SZ, Hock K, Schacter L (1995) Pharmacologic evaluation of high dose etoposide phosphate with g-csf administered as a 2 hour infusion daily × 2 in patients with solid tumors. Proc AACR 36:233
10. Gibaldi M, Perrier D (1982) Pharmacokinetics (2nd edn). Marcel Dekker, New York, pp 409–417

11. Kreis W, Rottach C, Budman DR, Chan K, Schulman P, Allen S, Weiselberg L, Vinciguerra V (1988) Pharmacokinetics and phase I evaluation of esorubicin (4'deoxydoxorubicin) by continuous infusion over forty eight hours in patients with leukemia. Cancer Res 48 : 5580–5584
12. Sessa C, Zucchetti M, Cerny T, Pagani O, Cavalli F, DeFusco M, DaJong J, Gentili D, McDaniel C, Prins C, Schacter L, Winograd B, D'Incalci M (1995) Phase I and clinical pharmacokinetic study of oral etoposide phosphate. J Clin Oncol 13 : 200–209
13. Thompson DS, Greco FA, Miller AA, Srinivas N, Igwenezue K, Hainsworth J, Schacter L, Kaul S, Barbhaiya R, Garrow C (1995) A phase I study of etoposide phosphate administered as a daily 30 minute infusion for 5 days. Clin Pharmacol Ther 57 : 499–507
14. Beckman G, Beckman L (1984) Human alkaline phosphatase isozymes, genetic variations and their relationship to natural selection. In: Stigbrand T, Fishermen WH (eds.) Human Alkaline Phosphatases, AR Liss, New York, pp 15–23
15. Horning SJ, Negrin RS, Chao NJ, Long GD, Hoppe RT, Blume KG (1994) Fractionated total body irradiation, etoposide and cyclophosphamide plus autografting in Hodgkin's disease and non-Hodgkin's lymphoma. J Clin Oncol 12 : 2552–2558
16. Köhl P, Köppler H, Schmidt L, Fritsch HW, Holz J, Pfluger KH, Jungclas H (1992) Pharmacokinetics of high dose etoposide after short term infusion. Cancer Chemother Pharmacol 29 : 316–320
17. Hande KR, Wedlund PJ, Noone RM, Wilkinson GR, Greco FA, Wolff SN (1984) Pharmacokinetics of high dose etoposide (VP-16–213) administered to cancer patients. Cancer Res 44 : 379–382
18. Newman EM, Doroshow JH, Forman SJ, Blume KG (1988) Pharmacokinetics of high dose etoposide. Clin Pharmacol Ther 43 : 561–564
19. Schwinghammer TL, Fleming RA, Rosenfeld CS, Przepiorka D, Shadduck R, Bloom E, Stewart C (1993) Disposition of total and unbound etoposide following high dose therapy. Cancer Chemother Pharmacol 32 : 273–278
20. Relling M, McLeod HL, Bowman LC, Santana V (1994) Etoposide pharmacokinetics and pharmacodynamics after acute and chronic exposure to cisplatin. Clin Pharmacol Ther 56 : 503–511
21. Mross K, Bewermeier P, Krüger W, Stockschlader M, Zander A, Hossfeld DK (1994) Pharmacokinetics of undiluted or diluted high-dose etoposide with or without busulfan administered to patients with hematologic malignancies. J Clin Oncol 12: 1468–1474
22. Freireich EJ, Gehan EA, Rall DP, Schmidt LH, Skipper HE (1996) Quantitative comparison of anticancer agents in mouse, rat, hamster, dog, monkey and man. Cancer Chemother Rep 50 : 219–245