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Unaltered pharmacokinetics after the administration of high-dose etoposide without prior dilution

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Summary. The pharmacokinetics of etoposide following a new method of administration was determined. Undiluted etoposide was given at a dose of 30 mg/kg as part an intensified conditioning regimen prior to bone marrow transplantation. A terminal half-life of 3.4 ± 0.7 h and a volume of distribution of 15.4 ± 9.6 l were found ($n = 8$); the AUC was 764 ± 302 μg h ml^{-1}. As compared with those obtained in other pharmacokinetic studies using etoposide diluted in normal saline, our data reflect full systemic bioavailability and unaltered pharmacokinetics. The application of undiluted etoposide makes the therapy easier and less time-consuming and avoids a high fluid volume and a high saline load.

Introduction

The probability of relapse after allogeneic bone marrow transplantation is up to 30% in standard-risk patients. Several investigators have tried to improve these results by combining total-body irradiation (TBI) and etoposide [1, 8, 10]. However, the application of etoposide is hampered by time-consuming dilution steps that result in the administration of large fluid volumes. It was realized more recently that the stability of etoposide in 0.9% saline and 5% dextrose is much greater than previously thought [5]. Lazarus et al. [2, 6] have suggested the use of etoposide without prior dilution. Since unchanged bioavailability has not been demonstrated for this procedure, we measured the pharmacokinetics of etoposide given as an undiluted solution.

Patients and methods

Eight patients with a high risk of relapse after allogeneic bone marrow transplantation were included in the present clinico-pharmacological study. Five suffered from acute lymphocytic ($n = 3$) or myeloid ($n = 2$) leukemia in second remission, and three exhibited chronic myelogenous leukemia in the accelerated ($n = 1$) or second chronic phase. The age of our patients ranged from 13 to 25 years (median, 20 years). The study was approved by the Ethical Committee of the University of Tübingen.

Etoposide (given on day -4; day 0 = day of marrow transfusion) was added to total-body irradiation (12 Gy given in 6 fractions on days -7, -6, and -5) and cyclophosphamide treatment (2 doses of 60 mg/kg given on days -3 and -2). Etoposide was given at a dose of 30 mg/kg by a 12-h infusion using a perfusor (Secura FT; Braun, Melsungen, FRG) equipped with a 50-ml syringe made of polypropylene (Number 87 2881/0; Braun, Melsungen, FRG), an infusion line made of polyvinylchloride (Number 87 2296/0; Braun, Melsungen, FRG), and a dual- or triple-lumen central venous catheter (Quinton, Seattle, Wash., USA). The equipment was prefilled with etoposide solution; rinsing with other fluids was avoided.

Determination of high-dose etoposide by HPLC. Particularly for high-dose pharmacokinetic investigations, a simple and rapid high-performance liquid chromatographic assay was developed that enabled the determination of etoposide levels in plasma for up to 48 h after the start of the infusion.

Sample treatment. Heparinized blood samples were collected from patients before treatment, at 4, 8, and 12 h during the infusion, and at 4, 8, 12, and 36 h following the infusion. Plasma was removed after centrifugation for 10 min and was immediately assayed or stored at –20° C until use.

Extraction and analysis. In a 1.5-ml microcentrifuge tube, 300 μl plasma was mixed with an equal volume of acetonitrile, vortexed, and deep-frozen at –20° C to achieve better deproteinization. After thawing, the sample was centrifuged for 5 min in a microcentrifuge at 12,000 *g*, and 20 μl supernatant was injected onto a high-pressure liquid chromatography system. Separation of etoposide was accomplished isocratically using a Hypersil-Phenyl column (10 μm, 250×4 mm, Shandon) and a mobile phase of water/methanol (50/50, v/v) containing 5 mM tetrabutylammonium phosphate at a flow rate of 1 ml/min. Etoposide was detected at 254 nm (UV).

Quantitation, calibration, recovery, and precision. For quantitation, the results of UV detection at 254 nm were used and showed sufficient sensitivity for the determination of etoposide levels following high doses. Quantitation was performed according to the external standard method by plotting the peak area against known concentrations of standards. Pharmacokinetic data were calculated with the aid of the TOPFIT program [4]; AUC values were calculated using the trapezoidal rule.

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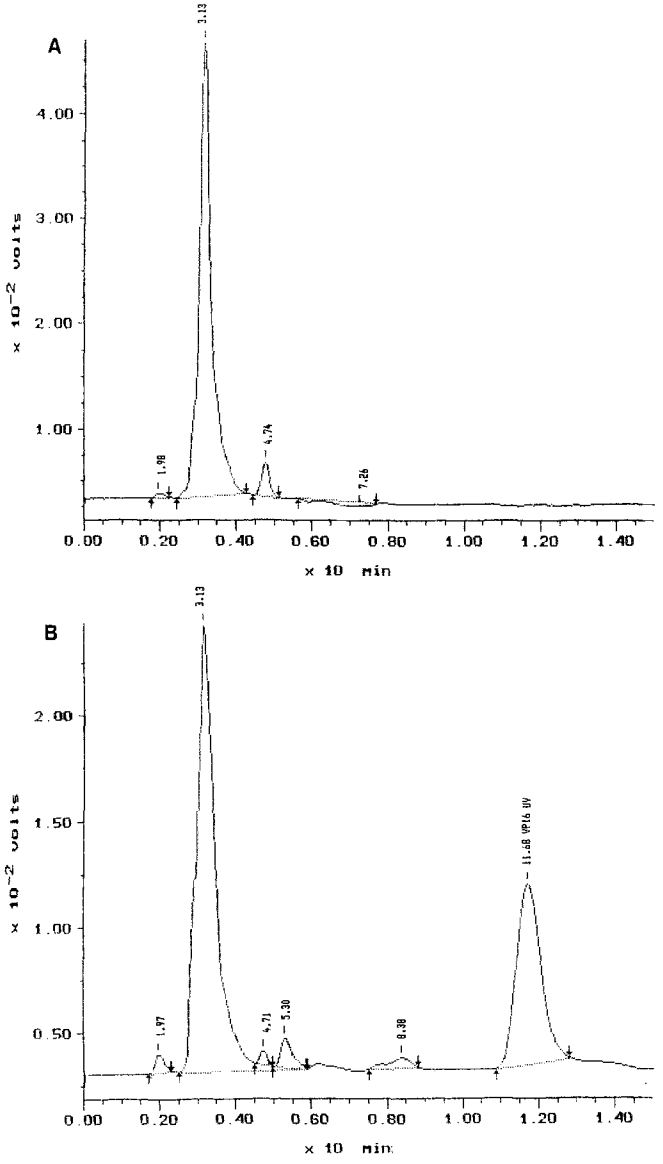

Fig. 1 A, B. HPLC chromatogram of plasma samples from patient UPN 146 after protein precipitation using acetonitrile. **A** Blank sample before treatment. **B** Sample at 8 h after the end of the etoposide infusion. Etoposide (*VP16*) shows a retention time of 11.68 min

Results

The standard curve for etoposide diluted in acetonitrile was linear in the range of 10–2,000 ng, with a correlation coefficient of 0.999 being observed. Extraction of etoposide from plasma yielded a recovery of 100% in all concentration ranges. The detection limit in plasma samples spiked with known concentrations of etoposide was 1,000 ng/ml plasma (20 µl extract injected) but could be increased up to 200 ng/ml (100 µl extract injected). The day-to-day reproducibility (coefficient of variation, CV) measured by independent analyses on 10 different days was 1.8% at 2,000 ng and 4.5% at 200 ng.

Figure 1 shows the chromatographic profile of plasma samples before and after etoposide administration. Plasma concentrations of eight patients at the end of a 12-h infusion were between 32.4 and 108.1 µg/ml. AUC values of 764 ± 302 µg h ml^{-1} (= 41.8 ± 18.4 [µg min ml^{-1}]/[mg m^{-2}]) were calculated for etoposide. The pharmacokinetic parameters were best described by two-compartment model. The results of the pharmacokinetics analyses are listed in Table 1.

Table 1. Pharmacokinetic parameters of undiluted etoposide given as a 12-h infusion

UPN	Dose (mg/kg)	Peak (µg/ml)	Half-life, terminal (h)	AUC (µg h ml^{-1})	Clearance (ml/min)	V_{dss} (l)
131	30	48.4	2.9	525	63.8	16
147	30	41.4	2.8	644	59.3	13.2
130	30	108.1	4	1,405	22.5	3.5
135	30	50.2	3.7	722	55.9	18.1
146	30	32.4	2.2	529	78.5	37.3
161	30	46.8	2.3	543	33.8	6.5
179	30	77.8	4.5	1,116	28.9	11.2
160	30	42.7	3.6	626	53.6	17.6
Mean		56	3.4	764	49.5	15.4
SD		23.2	0.7	302	18	9.6

V_{dss}, volume of distribution in steady state; UPN, unit patient number

Discussion

In the present pharmacokinetics study, we showed that etoposide can be given without prior dilution via a central venous catheter. The systemic availability was documented using a new simple, rapid HPLC method. In two other pharmacokinetics studies [3, 7] involving the administration of etoposide diluted in normal saline at a dose of 30–70 or 400–800 mg/m^2 for 3 consecutive days, the AUC values were reported to be 36.9 and 39.4 (µg min ml^{-2})/(mg m^{-2}), respectively. Our data of 41.8 ± 18.4 (µg min ml^{-1})/(mg m^{-2}) fit remarkably with those results, thus reflecting the full systemic bioavailability of undiluted etoposide.

The application of undiluted etoposide makes the therapy easier and less time-consuming and avoids a high fluid volume and a high saline load. Precipitations of etoposide were not detected as long as the infusion system had been prefilled with etoposide solution and rinsing with other fluids was avoided. In addition to these safety and practicability considerations, new schedules, which are attractive on the basis of a schedule-dependent activity [9] for etoposide, can now be more easily studied.

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