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ORIGINAL ARTICLE

Pharmacokinetic comparison of oral and intravenous etoposide in patients treated with the CHOEP-regimen for malignant lymphomas

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Abstract
Background The addition of etoposide to the CHOP protocol (CHOEP) has been shown to improve outcome in patients with aggressive non-Hodgkin's lymphoma. The intravenous administration of etoposide on three consecutive days represents a logistic problem and needs resources particular in the outpatient setting. This could be avoided by using etoposide capsules on days 2 and 3. However, the oral administration of cytotoxic agents is often affected by variable absorption and drug interactions.
Patients and methods We investigated the pharmacokinetic equivalency of oral and intravenous etoposide in ten patients (male, $n = 7$; female, $n = 3$; median age 56 years) with aggressive lymphomas. Treatment consisted of standard CHOP plus etoposide 100 mg/m^2 given intravenously on day 1, and 200 mg/m^2 orally on days 3 and 4. Samples from blood and urine were taken on days 1 (i.v. study) and 3 (p.o. study) before and after etoposide administration. Etoposide levels were determined by high-performance liquid chromatography (HPLC), and pharmacokinetic parameters were calculated with the TOPFIT computer program.
Results Mean peak plasma level after intravenous etoposide was significantly higher compared to oral administration (16.3 ± 3.7 vs. 12.0 ± 4.2 μg/ml; $P = 0.015$). The mean bioavailability of oral etoposide was 58 ± 15% with an interpatient variability of 26%. Significant differences of bioavailability of oral etoposide between the used dose levels (350, 400 and 450 mg) were not observed. Mean AUC after a 100 mg/m^2 intravenous and a 200 mg/m^2 oral dose of etoposide were 74.0 ± 18.3 and 84.9 ± 29.6 μg h/ml ($P = 0.481$). Interpatient variability of AUC was 25% for the intravenous route and 35% after oral intake. Urinary etoposide excretion as percentage of administered dose was 39.4 ± 10.6% after intravenous infusion versus 35.4 ± 9.4% after oral intake ($P = 0.422$). Renal clearance was also very similar with intravenous and oral route (18.5 ± 7.4 vs. 16.7 ± 6.6 ml/min; $P = 0.546$).
Conclusion The equivalency of AUC after 200 mg/m^2 of oral and 100 mg/m^2 of intravenous etoposide support the use of the oral preparation in patients treated with the CHOEP regimen, which makes the chemotherapy more convenient for the patients and help to reduce costs.

Keywords Lymphoma · CHOEP · Etoposide · Oral administration · Pharmacokinetics

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Introduction

For more than 30 years the CHOP regimen, consisting of cyclophosphamide, doxorubicin, vincristine and prednisone [15], is the basis for the treatment of malignant non-Hodgkin's lymphomas (NHL). CHOP is able to induce complete remissions (CR) in 45–80% of patients with aggressive

NHL, about 30–50% of them have the chance to be cured. Several studies evaluated more intensive combination regimens to improve the treatment results, nevertheless a large randomized multicenter trial failed to demonstrate a superiority of one of these protocols over CHOP [5].

In contrast, a more recent nation-wide German phase-III-trial found significantly improved response rates and event-free survival (EFS) for younger patients (<60 years) with aggressive NHL treated with CHOP plus etoposide 100 mg/m^2 intravenously (i.v.) on days 1–3 (CHOEP) [16]. Although this benefit of CHOEP over CHOP is not present in young low risk patients with CD20– positive lymphomas if rituximab is added to the chemotherapy [18], the etoposide-containing regimen should be used in CD20– negative NHL (peripheral T-cell lymphomas, PTCL; anaplastic-large cell lymphomas, ALCL) as well as in high-risk patients with diffuse-large-B-cell lymphomas (B-DLCL).

In the previous trials a dose of 100 mg/m^2 etoposide was given intravenously on three consecutive days. Because etoposide is available also as an oral (p.o.) preparation the question was, whether the intravenous treatment might be substituted by an oral administration, which would be more convenient for the patients and help to reduce treatment costs. However, in contrast to i.v. dosing the effects of oral etoposide are influenced by intestinal absorption processes and variable bioavailability. Furthermore, etoposide and the other cytotoxic drugs of the CHOEP regimen are substrates of the hepatic cytochrome-P-450-system, which could have an impact on the metabolism of the agent. Therefore the aim of our study was to investigate the pharmacokinetic equivalency of intravenous and oral etoposide within the CHOEP regimen.

Patients and methods

Patients and blood/urine sampling

Ten patients (male, $n = 7$; female, $n = 3$; median age 56 years) who were treated with CHOEP-chemotherapy because of newly diagnosed aggressive NHL were enrolled in a pharmacokinetic study after written informed consent had been obtained. Histological diagnoses included B-DLCL ($n = 6$), B-ALCL ($n = 1$), follicular lymphoma grade III ($n = 1$), Richter's syndrome ($n = 1$) and PTCL ($n = 1$). The patients were asked for taking part in the study, if they had received already at least three cycles of CHOEP with intravenous etoposide on days 1–3. All patients had normal renal and liver function. The study cycle of CHOEP consisted of intravenous cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 2 mg on day 1 and prednisone 100 mg orally for 5 consecutive days. Etoposide 100 mg/m^2 (patients received equivalent doses of Etopophos^{TM} 113.6 mg/m^2, Bristol–Myers Squibb, Munich, Germany) was given as an intravenous infusion for 60 min on day 1. After a wash out period of 24 h (day 2) the patient received single oral doses of 200 mg/m^2 etoposide each on day 3 and 4. This dose was based on a bioavailability of about 50% which was described in the product information, provided by the manufacturer, as well as in previous studies [6, 8, 21]. Due to the availability of capsules containing 50 or 100 mg etoposide (Vepesid^{TM} K 50 mg, K 100 mg), the individual oral doses were approximated in 50 mg steps. The capsules were taken by the patients in the morning after breakfast.

EDTA anticoagulated blood samples (5 ml, Sarstedt, Nurnberg, Germany) were collected before etoposide administration and 5, 10, 20, 30, 40, 60, 90, 120 and 150 min; 4, 6, 8, 12, 24, 48, 96, 120 and 144 h after infusion or taking capsules. The blood was centrifuged immediately at 5°C for 10 min, and the plasma was aliquoted into cryo vials. Urine collection was done at 4- to 6-h intervals until 24 h after the start of treatment. Plasma and urine samples were stored at –20°C until assayed.

The study protocol was approved by the Institutional Review Board of the University Hospital Dresden, Germany.

Measurement of etoposide concentrations in plasma and urine

Etoposide in plasma and urine was determined by high-performance liquid chromatography (HPLC) using liquid–liquid-extraction with 2 ml chloroform for sample preparation and online enrichment with an acetonitrile/water–triethylamine–acetic acid mixture 12%(V/V)/88% (V/V) [(water/triethylamine/acetic acid: 97.7%(V/V)/1.5% (V/V)/0.7625% (V/V); pH 5.6] applying a 8 × 3 mm 5 μ 120 C18 Nucleosil guard column from Machery & Nagel (Düren, Germany). The flow for the enrichment system was adjusted to 3 ml/min. An enrichment time of 3 min provided clean samples for the HPLC analysis, which was performed on a 250 × 4.6 mm 3 μ C18 Nucleosil analytical column (Machery & Nagel, Düren, Germany). The analytical eluent contains 33% acetonitrile and 67% triethylamine acetate. The flow in the analytical system was 0.4 ml/min. A fluorescence detector adjusted to 285 nm excitation and 320-nm emission was used for detection.

For quantification, the external standard method was used by linear regression analysis of five spiked plasma samples with 0.005, 0.05, 0.5, 5 and 10 µg/ml. This system has a detection limit of 5 ng/ml for etoposide using 1 ml of plasma or urine. Within-day variation was 9% for the lowest and 2% for the highest concentration. At the detection limit, the coefficient of variation was 9% for

plasma, as demonstrated by 10 measurements with spiked plasma. Between-day variation examined on 10 consecutive days with plasma spiked with 5 μg/ml of etoposide was 10%.

Pharmacokinetic parameters

Elimination half-life (t1/2), area under the concentration curve from zero to infinity (AUC) and maximum concentration (C_{max}) of etoposide in plasma were calculated using a 2-compartment model based on the TOPFIT computer program providing an optimized adaptation of coefficients of variation between the observed and calculated respective data [10]. For the i.v. application of etoposide an optimal regression coefficient >0.91 was found in all patients by using a linear two compartment model described by the equation:

$$\mathrm{Cp} = ae^{-\alpha t} + be^{-\beta t}$$

The pharmacokinetic parameters for the oral application of etoposide were calculated using a linear two-compartment model assuming a classical first-order absorption constant described by the equation:

$$\mathrm{Cp} = ae^{-\alpha t} + be^{-\beta t} - ce^{-kat}$$

with Cp = plasma concentration at a specific time point, t = time, a to c = dimensionless coefficients required to describe the time-course in a specified compartment, α and β = elimination rate constants, k_a = absorption rate constant. Absorption half-life (t1/2abs) was calculated as $\ln 2/k_a$. The regression coefficient for all oral applications analysed were >0.93.

The total clearance (Cl_{total}) was calculated by the equation:

$$Cl_{total} = \mathrm{dose}/AUC_{inf}$$

It should be noted, that the total clearance includes also the fraction of orally administered drug, which is not absorbed but is directly excreted by the faeces (total "body" clearance).

Renal clearance was calculated by the equation:

$$Cl_{renal} = k_{renal} \cdot V_d$$

with k_{renal} = renal elimination rate constant, V_d = distribution volume.

As a weighting function for the measured data $1/y$ was used. The interpatient variability of pharmacokinetic parameters was evaluated by determining of the coefficient of variation (CV = SD/mean × 100).

Statistical analysis

The statistical analysis was performed using software Excel and SPSS for Windows. Pharmacokinetic parameters are presented as means and standard deviation (±SD) if not otherwise indicated. Statistical comparisons were made using Mann–Whitney U test. Differences were considered statistically significant a P value < 0.05.

Results

The absolute doses of etoposide, which were administered to the patients ranged from 166 to 220 mg for the intravenous route and 350–450 mg for the oral route, corresponding to mean doses of 101 and 203 mg/m^2, respectively.

Mean peak plasma level after intravenous etoposide was significantly higher compared to oral administration (16.3 ± 3.7 vs. 12.0 ± 4.2 μg/ml; P = 0.015). Maximum concentration of intravenous etoposide occurred in all patients between 30 and 60 min after start of infusion. After oral administration the mean t_{max} (±1 SD) was at 1.5 ± 1.2 h (range, 0.3–4.1 h). Decay curves of mean plasma levels for intravenous and oral route are presented in Fig. 1.

Mean $t1/2_{abs}$ was calculated with 0.9 ± 0.5 h (range 0.2–1.9 h), however there was a high interpatient variability of 55%. The mean bioavailability (±1 SD) of the oral etoposide was 58 ± 15% (range 29–84%). The interpatient variability of bioavailability was 26%. The (mean) bioavailability after intake of 350 mg (n = 4), 400 mg (n = 5) and 450 mg (n = 1) was 56, 60 and 56%, respectively.

The calculated AUC achieved following the intravenous and oral etoposide dose in each patient is shown in Fig. 2. The mean AUC (± 1 SD) after a 100 mg/m^2 intravenous and a 200 mg/m^2 oral dose of etoposide were 74.0 ± 18.3 μg h/ml (range 43.8–104.8 μg h/ml) and 84.9 ± 29.6 μg h/ml (range 43.8–141.4 μg h/ml), respectively. This difference was not statistically different (P = 0.481). Interpatient variability was 25% for the intravenous route and 35% after oral intake.

The volume of distribution in steady state was also not statistically different between the two routes of administration (14.5 ± 2.5 l vs. 16.8 ± 4.3 l; P = 0.315). Urinary etoposide excretion as percentage of administered dose was 39.4 ± 10.6% after intravenous infusion versus 35.4 ± 9.4% after oral intake (P = 0.422). The time course of etoposide urine elimination is presented in Fig. 3. The renal clearance was not different between intravenous and oral route (18.5 ± 7.4 vs. 16.7 ± 6.6 ml/min; P = 0.546). Due to the higher oral dose of etoposide the total clearance after oral

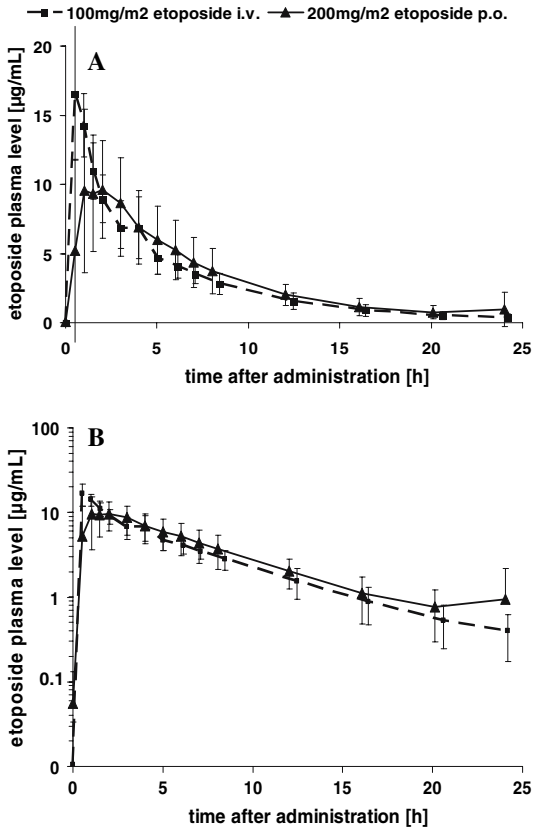

Fig. 1 Decay curve of etoposide plasma levels (mean ± SD) after infusion of 100 mg/m^2 or oral administration of 200 mg/m^2 within the CHOEP regimen (n = 10; **a** linear depiction, **b** logarithmic depiction)

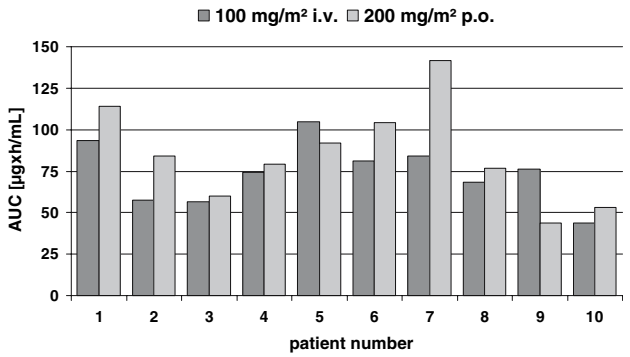

Fig. 2 Individual AUC in patients after infusion of 100 mg/m^2 or oral administration of 200 mg/m^2 within the CHOEP regimen (n = 10)

intake was found about 2-fold higher compared to the intravenous administration (84.4 ± 30.5 vs. 45.5 ± 10.3 ml/min). Intrapatient comparisons for urine etoposide and renal clearance are illustrated in Fig. 4.

Terminal elimination half-life was longer after intake of capsules than after infusion (5.7 ± 1.7 vs. 4.3 ± 0.5 h, P = 0.052).

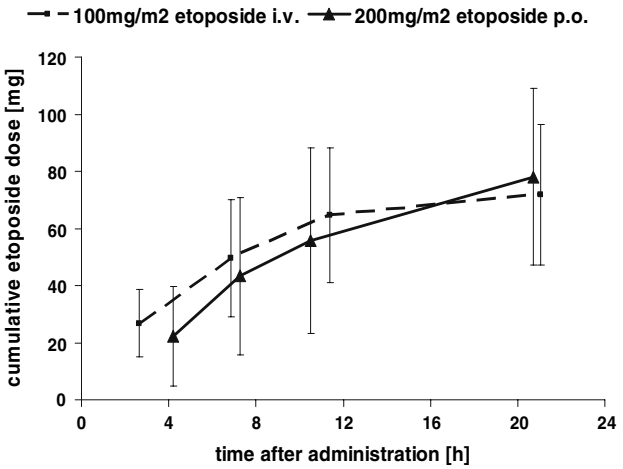

Fig. 3 Cumulative doses (mean ± SD) of etoposide in urine after infusion of 100 mg/m^2 or oral administration of 200 mg/m^2 within the CHOEP regimen (n = 9)

Discussion

The CHOEP regimen has been demonstrated as a highly effective regimen in patients with aggressive lymphoma by a number of clinical trials [1, 13, 14, 16, 18, 23]. However the administration of this regimen is more complex compared to CHOP because etoposide has to be given intravenous on three consecutive days, representing a disadvantage particular in the out patient setting.

A Swedish clinical phase II study already investigated a regimen consisting of CHOP plus intravenous etoposide on day 1, followed by oral doses of 200 mg/m^2 on days 2 and 3 (CHOP-E), in 132 adult patients with previously untreated NHL [2]. Regarding different inclusion criteria in terms of age, risk groups and histology a comparison of this study with the results from the large randomized German CHOEP trials [16, 17], which exclusively used the intravenous etoposide, did not indicate a substantial loss of antineoplastic efficacy or increased toxicity after oral drug administration. Gastrointestinal or liver toxicities were very infrequent. However, the oral administration of cytotoxic drugs is associated with variable AUC because the agents have to be transported across the intestine, then pass the liver and enter the systemic plasma circulation. Therefore, before using oral etoposide in the CHOEP regimen routinely, the pharmacokinetic equivalency should be evaluated in this study.

Previous studies in cancer patients have indicated a considerable dose dependency of absorption after oral etoposide [8, 9, 20], with reduced bioavailability and a non-linear increase of AUC in total doses greater than 200 mg. In our patients the mean (and median) bioavailability was 58% (range, 29–84%), and there was no evidence for an impaired absorption at the used dose level.

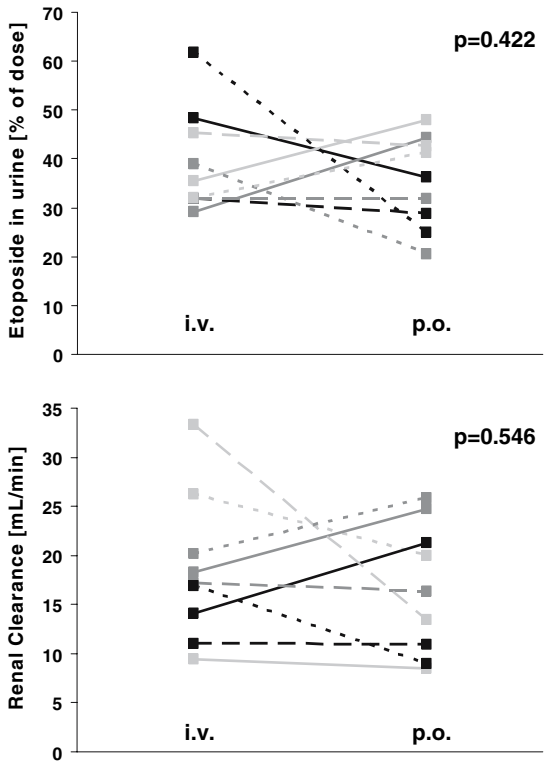

Fig. 4 Intrapatient comparisons (n = 9) for urine etoposide and renal clearance after infusion of 100 mg/m^2 or oral administration of 200 mg/m^2 within the CHOEP regimen

Other studies [3, 8, 12] have reported mean bioavailabilities of 38–62% (ranges, 22–79%) after intake of 300 mg and 400 mg etoposide, respectively, which are very similar to the results in the present series. The interpatient variability in our cohort of 26% was also not different from the data observed in these trials (28–38%). Poor chemical stability of etoposide in gastric and intestinal fluids, influences of the intestinal mucosa on the absorption process, first pass effect and variable drug metabolism are discussed as background for variable bioavailability [22].

AUC is the most important parameter to compare drug effects after different routes of administration. To avoid a negative impact on therapeutic efficacy the patients were included in this study only after they had received at least three cycles of chemotherapy with total intravenous etoposide administration. However, our data very stringent indicate the pharmacokinetic equivalency of intravenous and oral etoposide in the CHOEP regimen. Interpatient variability of AUC was higher after oral intake (35%) compared to the intravenous route (25%). This corresponds to studies, which evaluated intravenous and oral doses of 50 mg and 100 mg/m^2 and found a 1.5- to 3-fold higher interindividual variation of AUC among orally treated patients [7, 24]. This variability is mainly due to inconstant absorption. However, the impact of drug metabolism on AUC variability is not yet well defined. Whether there is an impact from the intestinal CYP3A4, which is activated by etoposide absorption is hypothetical. This isoform of cytochrome P450 can be found in the intestinal mucosa with substantial activities of about 50% of those expressed in the liver [4, 11]. For urinary etoposide elimination, which was about 35–40% of dose, and renal clearance we found very similar results after both routes of administration. Because total clearance strongly depends on dose administered (Cl_{total} = AUC/dose), it was found about twofold higher after oral intake.

The results from our study for peak plasma concentration, steady-state volume of distribution and terminal half-life after oral and intravenous etoposide are in accordance with previous reports [19, 22]. Altogether there is no evidence for an altered pharmacokinetic profile of oral etoposide administered in a combination regimen with doxorubicin, cyclophosphamide, vincristine and prednison.

From a pharmacoeconomic point of view the use of oral instead of intravenous agents is often recommended due to lower costs. However, etoposide capsules are expensive in Germany. Intravenous etoposide 100 mg/m^2 on day 1 followed by two days of 350 mg oral drug (corresponding to 200 mg/m^2) for a standard patient of 1.80 m^2 body surface area are charged with about 410 EUR, whereas for the same patient a complete intravenous dosing (100 mg/m^2 day 1–3) costs 260 EUR. If etopophos is used, due to its improved pharmacological properties, the corresponding prices are 440 EUR and 350 EUR. Therefore, the use of oral etoposide in the CHOEP regimen is more economic only if the patient can be treated at home, which reduces the costs for hospital stay or outpatient visit and venous access.

In conclusion the results of this pharmacokinetic study support the use of oral instead of intravenous etoposide in patients who are treated with the CHOEP regimen for non-Hodgkin's lymphoma. The equivalency of clinical efficacy and toxicity is suggested by comparing studies using the different routes of administration; however, could be proven only by a randomized trial. An alteration of pharmacological effects by the additional use of rituximab in patients with CD20+ B-cell lymphoma can be widely excluded, because the monoclonal antibody is exclusively eliminated via specific binding on CD20+ B-cells.

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