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Clinical report

Population pharmacokinetic approach to compare oral and i.v. administration of etoposide

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The antitumor effect of etoposide (ETO) may be related to duration of exposure to a relatively low serum level while myelosuppression may be dependent on peak ETO serum levels. With regard to such therapeutic ranges, duration of exposure to predefined plasma ETO concentration ranges and the related AUC (expressed as percent of total AUC, pAUC) were used to compare pharmacokinetic profiles after oral and short time i.v. (1 h infusion) administration of identical ETO doses (100 mg/m^2). Patients included in this study received i.v. (18 patients, short-term infusions) or oral (16 patients) ETO on different treatment schedules. Plasma ETO concentrations were determined by HPLC and population pharmacokinetic parameters were calculated (P-Pharm 1.4). Despite an 'apparent bioavailability' of 59%, oral administration of ETO was associated with the same time of exposure to a predefined 'therapeutic range' of 0.5–3 mg/l and a significantly higher pAUC compared to i.v. administration. By contrast, time of exposure to the probably more myelotoxic concentration range above 3 mg/l was significantly shorter and the related pAUC was highly significantly lower after oral than after i.v. administration. These findings demonstrate that oral ETO therapy is at least equivalent to short time i.v. therapy in terms of achieving specific target concentration ranges and avoiding peak concentrations. [© 1999 Lippincott Williams & Wilkins.]

Key words: Etoposide, intravenous, oral, population pharmacokinetics, schedule dependency.

Introduction

Etoposide (ETO) is one of the most frequently used chemotherapeutic agents in pediatric and adult oncology as a single agent as well as in combination with other anticancer drugs. ETO acts by inhibition of DNA topoisomerase II. This enzymatic inhibition is reversible, saturated at high concentrations, cell cycle specific, probably concentration dependent and leads to an accumulation of cells in G_2/M.[1,2] Thus, prolonged ETO administration produces longer periods of topoisomerase II inhibition by virtue of prolonged exposure to a critical concentration (not precisely determined) and would be expected to lead to greater cytotoxicity when compared with the short-term administration of high concentrations.[3] While findings using *in vitro* systems have demonstrated that cytotoxicity is related to both concentration and duration of exposure to ETO, schedule dependency could not be shown *in vitro*.[4–7]

In vivo, however, ETO is one of the few anticancer drugs for which a marked schedule dependency has been shown. This is especially true for small cell lung cancer (SCLC), a highly chemosensitive tumor type, and the situation is probably similar in other sensitive neoplasms. The drug displayed an improved therapeutic index when repeated lower doses were given over prolonged periods of time rather than one single higher dose.[8] Further studies have shown the activity of even more prolonged schedules of administration both i.v. and orally, and high response rates have been reported (reviewed in Greco and Hainsworth[3] and Joel and Slevin[9]).

However, randomized studies with repeated or prolonged ETO administration in other tumor types are needed to confirm these observations and the activity of the prolonged schedules has to be tested against standard dosing in clinical trials.

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Pharmacokinetic analyses suggested that the improved therapeutic index of such ETO schedules results from prolonged maintenance of low plasma levels of ETO.[8,10] Tumor cytotoxicity of ETO appears to depend more on relatively low critical concentrations than on the magnitude of the peak plasma concentration. On the other hand, some data suggest that high peak levels (i.e. greater than 5-10 mg/l) are most often associated with more severe myelosupression. A much lower daily dose given for a prolonged period is less myelotoxic than the high-dose brief schedule but may be at least as cytotoxic to selected sensitive tumors.

Thus, the mechanism of ETO cytotoxicity favors using a prolonged schedule. Such a schedule, however, has not yet been defined. So far, there are three possible ways of prolonged treatment: i.v. infusion, repeated short-time infusions and oral drug therapy with daily or even more frequent administration of the drug. Continuous i.v. infusion is only feasible in the hospital for a limited period of time. For reasons of stability and low water solubility, ETO cannot be given by continuous i.v. pump in an outpatient setting. Consequently, only two methods are at present appropriate under outpatient conditions. Both repeated short-time infusions and oral therapy allow treatment durations of weeks or even months. Oral administration has turned out to be a feasible way of administering ETO on an outpatient basis, avoiding the discomfort and cost of hospitalization. The use of oral ETO in adults has recently been reviewed by Hainsworth and Greco who concluded that prolonged oral ETO therapy was both feasible and relatively well tolerated.[11] Low-dose oral ETO for pediatric tumors is well tolerated; disease stabilization and an useful palliative effect were noted.[12-14]

One important treatment-relevant factor of ETO is its pharmacokinetic variability. With i.v. administration the pharmacokinetic parameters of ETO are known to show marked interindividual variability, whereas intrapatient variation has been reported to be low.[15,16] Objections have been raised arguing that oral ETO might be less reliable than the same dose administered i.v. based on the assumption that a changing bioavailability increases the variability of the overall AUC to an unacceptable degree.[11,17]

Plasma levels as related to dose, schedule and tumor responsiveness have been evaluated in several studies. For SCLC, different studies suggest that a low steady-state plasma ETO concentration (0.5-1 mg/l) is associated with cytotoxic activity.[3,8,10,18] The critical concentration for an 'adequate' inhibition of topoisomerase II appears to be below 1 mg/l in SCLC; minimal plasma levels for other tumor types remain to be determined.

Higher peak levels (i.e. above 5-10 mg/l) are frequently associated with more pronounced myelosuppression than are lower peak levels, and they are not what prolonged therapy aims for. Clark, Slevin and their group[19] found the duration of exposure to plasma ETO above 3 mg/l to be predictive of nadir neutrophil count and the duration of exposure to plasma ETO above 2 mg/l to be predictive of nadir white blood cell (WBC) count in SCLC. The quantitative relationship between the extent of myelosuppression and steady-state concentrations during infusion (72 h infusion, 125 mg/m^2/day) was calculated in a population model: the typical response profile is characterized by the half-maximal effect of hematologic toxicity (i.e. decrease to 50% of baseline WBC count) after exposure to c_{50}=3 mg/l ETO over 3 days.[15] The leukopenic effect of ETO may also show differences according to tumor species and patient populations.

Based on the hypothesis that ETO cytotoxicity favors the application of a prolonged schedule, the present study is conducted to determine reliable criteria of selecting either of the two alternatives, i.e. repeated short time infusions or daily or even more frequent oral administrations. In order to find the most appropriate schedule and to predict ETO efficacy it will not suffice to compare doses or to achieve certain AUC values, but it will be more important to compare the different pharmacokinetic profiles. In the present study, two pharmacokinetic parameters were used to compare plasma profiles after oral and i.v. administration of ETO, i.e. duration of exposure to specified plasma ETO concentration ranges and the AUC as an indicator for exposure to a drug in predefined ranges. In accordance with results of Slevin[8] and Greco,[3] a serum level below 0.5 mg/l was defined as low, 0.5-3 mg/l as intermediate, and serum levels greater than 3 mg/l as high and possibly primarily toxic.

Materials and methods

Patients

Eighteen patients had short-time infusions of ETO (Table 1, 67-200 mg/m^2, no concomitant carboplatin).[21] Sixteen patients received ETO orally at a dosage of 28-149 mg/m^2 in combination with oral trofosfamide for palliation (Table 2).[20] Within 24 h, an average of five blood samples were withdrawn after i.v. and eight after oral administration, sampling times have been reported elsewhere.[20,21] Informed consent was obtained from all patients and/or their parents. All plasma concentration data were normalized to a dose of 100 mg/m^2 given orally or i.v., respectively.

Analytical method

ETO concentrations in the plasma were determined by reversed-phase HPLC in combination with fluorescent detection or electrochemical detection.[22] The limits of detection were 200 and 25 ng/ml, respectively; the coefficients of variation for intra-assay variability were less than 2 and 7%, respectively.

Table 1. Patients treated with ETO i.v. within different schedules (1 h infusion)

Patient no.	Age (years)	Sex	Dose (mg/m^2)	Diagnosis
1	0.8	M	120	AML
2	1	F	100	AML
3	9	F	150	AML
4	15	F	125	AML
5	2	F	67	AML relapse
6	5	F	100	AML relapse
7	8	F	150	ALL
8	14	M	150	ALL
9	16	M	150	ALL
10	16	F	150	ALL
11	14	M	150	ALL
12	11	F	150	ALL relapse
13	10	M	125	Hodgkin's disease
14	1	F	80	PNET
15	2	M	200	LCH
16	14	M	150	Ewing's sarcoma
17[a]	16	F	150	rhabdomyosarcoma
18	17	M	120	osteosarcoma
Median	10.5		150	
Range	0.8–17		67–200	

[a]Patient had a 2 h infusion.

Pharmacokinetic analysis

The statistical pharmacokinetic program P-Pharm, Version1.4,[23] was used to determine the population parameters of ETO. For i.v. data, initial population parameters and variances were estimated by a simplex procedure of a dummy patient, using a proportional error model. For oral data, parameters from the first seven patients were used to develop initial population priors and variances, applying a homoscedastic error model. Subsequently, a Bayesian algorithm was taken to estimate the final individual parameters of all patient data sets. Based on these estimated individual pharmacokinetic parameters, multiple concentration versus time data sets per patient were calculated using TOPFIT.[24] In a further step these *x/y* data sets were taken to calculate the duration of ETO plasma concentrations within specified ranges. As only few concentration versus time data per patient were available, calculated individual *x/y* data sets were also used to calculate total AUC by non-compartmental analysis.[24] The AUC relating to specified concentration ranges (expressed as percent of total AUC, pAUC) was calculated as sum of area under data (AUD, non-compartmental analysis[24]) and according rectangles (compare Figure 1).

The means of the population parameters (i.e. a 'typical' subject) were used to simulate different administration schedules reported in the literature and to calculate duration of plasma concentrations above predefined ETO concentrations.

Table 2. Patients treated with oral ETO

Patient no.	Age (years)	Sex	Dose day 1 (mg/m^2)	Diagnosis
1	25	M	111.1	CML (Ph+)
2	3	M	71.43	hepatoblastoma
3	7	F	111.1	Wilms' tumor, third relapse
4	18	M	81.5	Ewing's sarcoma, left femur, relapse
5	18	M	62.5	testicular teratoma, third relapse
6	20	F	148.8	Ewing's sarcoma, left humerus, second relapse
7	21	F	125.0	PNET,[a] chest wall, relapse
8	58	F	90.9	breast cancer, relapsed, metastatic
9	73	F	88.2	ovarian carcinoma, relapse
10	4	M	37.3	neuroblastoma
11	7	F	54.9	embryonal rhabdomyosarcoma
12	7	M	54.3	Ewing's sarcoma
13	12	F	41.6	rhabdomyosarcoma
14	18	F	78.9	Ewing's sarcoma
15	26	M	27.8	Ewing's sarcoma
16	37	F	85.2	cervical carcinoma
Median	18		80.2	
Range	3–73		27.8–148.8	

[a]Primitive neuroectodermal tumor.

$AUC_{(conc\ 0.5–3)} = AUD_{(conc\ 0.5–3)} + AUD_{(conc\ 3–0.5)} + R_1–(R_2+R_3)$

$pAUC_{(conc\ 0.5–3)} = AUC_{(conc\ 0.5–3)} / AUC_{total} * 100$

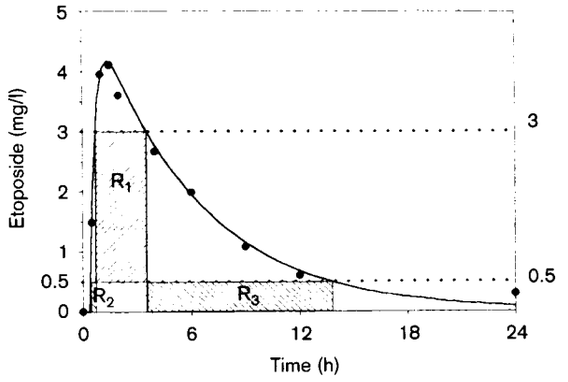

Figure 1. Calculation of AUC within a given concentration range. AUD, area under data: R, rectangle.

Statistical analysis

Wilcoxon's signed rank test was applied to compare time of exposure and pAUC after oral and i.v. administration.

Results

Clinical characteristics of the two populations are shown in Tables 1 and 2.

Pharmacokinetic parameters

ETO concentration versus time data after i.v. administration were appropriately described by a linear two-compartment model, while a one-compartment model with first-order absorption was accurate for oral administration. Population estimates and their standard deviations (SD) are reported in Table 3.

Duration of exposure to plasma concentrations in different concentration ranges

There were no statistically significant differences in the time of exposure to ETO concentrations below 0.5 mg/l and concentrations of 0.5–3 mg/l after i.v. or oral doses of 100 mg/m^2. Times of exposure to ETO concentrations above 3 mg/l were significantly shorter after oral than after i.v. administration of the same dose. The interindividual variability in the different concentration ranges was about 1.5- to 2-fold higher after oral compared to i.v. administration (Table 4).

Table 3. Population pharmacokinetic parameters of ETO after i.v. and oral administration

Parameters	ETO i.v. two-compartment model, error 1/*y*	ETO oral one-compartment model, error homo
CL (ml/min/m^2)	24.0 ± 0.33	43.3[a] ± 1.04
V_c (l/m^2)	3.71 ± 0.57	12.2[b] ± 4.86
k_a (h^{-1})		3.34 ± 3.30
Lag time (h)		0.308 ± 0.337
K_{12} (h^{-1})	0.348 ± 0.117	
K_{21} (h^{-1})	0.529 ± 0.129	

Abbreviations: CL, total body clearance, *K*, transfer rate constant; SD, standard deviation; V_c, central volume of distribution; k_a, rate of absorption; lag time, lag time of absorption.
[a]Apparent oral clearance CL/*f*.
[b]V_c/f.

Area under the curve

The mean total AUC was 72.2 ± 16.7 mg/l·h/100 mg/m^2 after i.v. and 42.4 ± 14.7 mg/l·h/100 mg/m^2 after oral administration (mean ± SD), at a calculated mean 'apparent bioavailability' of 59%. The interindividual variability was about 1.5-fold higher after oral than after i.v. administration.

For a differentiated view, pAUC values in predefined concentration ranges were considered separately: after i.v. administration a significantly higher pAUC was found at ETO concentrations above 3 mg/l, whilst the pAUC was significantly lower with levels below 0.5 mg/l and in the 0.5–3 mg/l range (Figure 2 and Table 4). The variability of pAUC after oral administration was about 2-fold higher compared to i.v. in the low and intermediate concentration range, whereas an about 8-fold higher variability was found with ETO concentrations above 3 mg/l.

Discussion

Prolonged ETO therapy can be superior to short-term administration under certain conditions. Prolonged therapy offers the possibility to treat patients on an outpatient basis either by repeated short-term infusions in the outpatient department or by oral therapy. The latter is the most convenient option for the patient. However, when using drugs with only a small therapeutic window, there is always uncertainty about intra- and interindividual variability within a given

Table 4. Duration of exposure (h), AUC total and pAUC (% of total AUC) after the administration of 100 mg/m^2 ETO either i.v. or orally within different concentration ranges (median/mean, CV in brackets)

Concentration range (mg/l)	i.v.	Oral	p^a
Duration of exposure (h)			
<0.5	6.9/7.1 (48.0%)	8.0/8.0 (62.0%)	0.6
0.5–3	10.1/9.7 (17.7%)	10.5/11.1 (36.2%)	0.3
>3	7.2/7.2 (26.8%)	5.7/5.6 (33.0%)	0.05
AUC total (mg·h/l/m^2)			
AUC total	70.6/72.0 (23.2%)	42.1/42.4 (35.0%)	
pAUC (% of total AUC)			
<0.5	14.7/14.5 (14.3%)	23.9/24.4 (31.8%)	<0.001
0.5–3	36.6/37.2 (7.7%)	55.6/54.7 (16.8%)	<0.001
>3	49.4/48.3 (9.3%)	12.4/21.1 (73.2%)	<0.001

[a] p values for comparison of i.v. and oral data, respectively (Mann–Whitney rank-sum test).

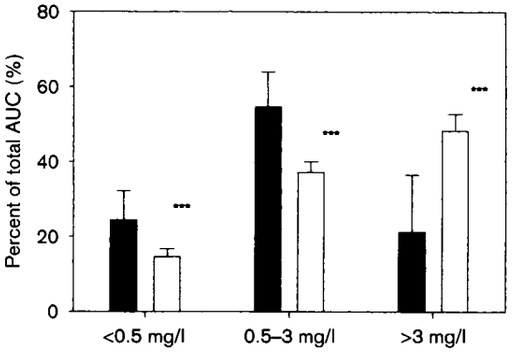

Figure 2. Duration of exposure within different etoposide concentration ranges after i.v. (open bars) and oral (solid bars) administration of 100 mg/m^2, respectively. p values for comparison resulting from Mann–Whitney rank-sum test (***$p \leq 0.001$).

treatment course. Oral treatment schedules must therefore fulfil hard criteria. On the one hand, they must be comparable to i.v. chemotherapy as to assure effectiveness. On the other hand, as they are used under outpatient conditions, they must provide safety and the administration of the drug should be as convenient as possible for the patients.

Comparability

In the present study two pharmacokinetic criteria, i.e. duration of exposure to specified plasma ETO concentration ranges and pAUC in the same predefined ranges, were used to compare oral and i.v. administration of ETO. Naturally, oral administration of 100 mg/m^2 ETO, when compared to i.v. administration of an identical dose, leads to lower total patient exposure as measured by the total plasma ETO AUC (mean AUC after oral administration was about 59% of the mean AUC after i.v. infusion). On the other hand, oral administration was found to be associated with the same time of exposure to a predefined 'therapeutic range' of 0.5–3 mg/l. The pAUC in this range was even higher after oral than after i.v. administration. At concentrations above 3 mg/l, however, which are associated with more severe myelosuppression, oral administration went along with a significantly lower time of exposure and pAUC than i.v. infusion.

The heterogeneity of the patient population available for our calculations might be a possible drawback of this evaluation. However, the pharmacokinetic parameters and the values for interindividual variability with i.v. administration of ETO are in good agreement with results reported in the literature for adults[19] (reviewed in Henwood and Brogden[16]) and children.[25–28] The data support the assumption that pharmacokinetic characteristics in children are similar to those seen in adults. The pharmacokinetic results after oral administration of ETO are comparable with data reported in the literature.[14,28–32] Granted that no patient received ETO both orally and i.v., the comparison of the AUC after oral and i.v. administration in different patients, i.e. a calculated 'apparent bioavailability' of 59%, is consistent with other reports suggesting a bioavailability of around 50–70%.[33–35] After oral administration of ETO, the interindividual variability of total AUC was higher than after i.v. administration. To some extent this may have been influenced by the high range of oral doses administered in the present study, as the bioavailability of ETO is supposed to be superior with lower oral doses. After i.v. administration of ETO, the duration of ETO plasma concentrations above specified levels were calculated for adults[8,9,19,36,37] and children,[28] and data were correlated to pharmacodynamic parameters. In order to compare our results with pertinent data from the

literature, the means of pharmacokinetic parameters from our population analyses were applied to model a 'typical' subject and simulate different schedules reported in the literature.

On this basis, times of exposure were calculated for schedules reported by Clark *et al.*[19] (100 mg/m^2/day by 2 h infusion on 5 consecutive days or 62.5 mg/m^2/day by 75 min infusion on 8 consecutive days). Times of exposure to ETO concentrations greater than 1, 5 or 10 mg/l based on our population were about 70–84% of the values reported by Clark *et al.* A higher clearance rate (24 ml/min/m^2) and shorter terminal half-life (3.8 h) in our population may explain these differences (Clark: 5 day regimen, 18.2 ml/min/m^2 and 6.4 h; 8 day regimen, 19 ml/min/m^2 and 5.9 h). In another study reported by Pinkerton *et al.*,[28] children received a schedule similar to ours (100–150 mg/m^2 by 1 h infusion). Mean terminal half-life in our population (3.8 h) was comparable to the data reported by Pinkerton *et al.* (4.2 h). Similarly, intervals of plasma concentrations above 1, 5 and 10 mg/l in our population (125 mg/m^2/1 h: 13.8, 5.4 and 2.5 h) were about the same as reported by Pinkerton *et al.* (14.7, 7.7 and 2.5 h).

Various authors reported pharmacokinetic analyses to calculate achievement of potentially therapeutic and moderately myelosuppressive plasma ETO concentrations with oral administration in adults[14,31,32,38–40] and children.[28] Schwartsmann *et al.*[32] summarized a study where ETO was administered at a schedule of 25 mg/m^2 orally, twice a day for 7 days, and reported a terminal half-life of 3.2 h and clearance of 30 ml/min/m^2. Our population who showed a comparable terminal half-life of 3.6 h and somewhat higher clearance of 43.4 ml/min/m^2 reached about 77% of the exposure to plasma concentrations greater 1 mg/l reported by those authors. Comparison with other published data was difficult as authors tended to report absolute numbers rather than doses related to square meters of area[39] or no pharmacokinetic parameters were reported.[40]

The 'therapeutic window'

For clinical purposes, the definition of the minimal effective ETO level is based on the work of Clark *et al.*[19] and Johnson *et al.*[41] These data, however, were obtained from studies of patients with SCLC. Although the effectiveness of low-dose ETO has been shown for many other entities, the upper limit has not been clearly defined for all tumor types. Still, as it is obvious that oral therapy is inappropriate for high-dose schedules, the aim is to maintain effective serum levels continuously, rather than to achieve high levels for a short period. As the 'therapeutic window' may vary depending on the tumor type, the optimal concentration range and dose must be found for each tumor type separately. If different serum levels have to be achieved, the dose can be varied up to 200 mg without qualitatively changing the percentage of the pAUC and duration of exposure values, as a linear pharmacokinetic behavior of oral ETO up to 200 mg was shown.[42] When oral doses are further increased, the percentage of ETO absorbed will go down while the coefficient of variation in oral ETO bioavailability increases.[34]

Conclusions

Long-term therapy has its place in maintenance therapy where it possibly eradicates minimal residual disease following intensive treatment, in the treatment of tumors with a low turnover and in the setting of palliative therapy. For such long-term ETO therapy oral administration is an attractive option. The target of stable serum levels is at least as well achieved by oral administration as through repeated short time infusions. The pAUC for medium serum levels is significantly higher with oral administration. Therefore, higher and possibly toxic ranges can be avoided more effectively. Greater tissue exposure to ETO may be associated with greater cytotoxicity within this compartment. As there is marked inter-patient variability, but relatively little intra-patient variation, ETO is a suitable drug for pharmacokinetically guided dosing.[27] Limited sampling models might ensure that plasma levels of ETO are not being exceeded, resulting in greater reproducibility and, thereby, in an improved therapeutic index. Future studies related to this topic should correlate the pharmacodynamic results to duration of exposure to ETO plasma concentration ranges and AUC levels in such predefined concentration intervals rather than to overall AUC. Thus, it may be possible to find the optimal 'therapeutic window' and to optimize drug dose and scheduling. Well-defined serum ranges which may need to be specified for each tumor type separately will be the appropriate basis for this procedure. In first-line therapy, however, it is unlikely that prolonged oral ETO will offer any advantage over intermittent systemic treatment, since alternative approaches will have a higher priority.

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