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Drug monitoring of etoposide (VP16-213)

Correlation of pharmacokinetic parameters to clinical and biochemical data from patients receiving etoposide

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Summary. Pharmacokinetic parameters established in 15 patients receiving parenterally administered etoposide (80–120 mg·m^{-2}) are reported. The etoposide assay by means of mass spectrometry after sample separation by thin-layer chromatography or high-pressure liquid chromatography used in this study has been described elsewhere [4]. Peak plasma levels (9.5–63.3 μg·ml^{-1}), the area under the curve (AUC) (2707–10192 μg·ml^{-1}·min^{-1}), the mean transit time MTT (2.7–10.6 h), etoposide half-lives t½α (0.10–0.52 h) and t½β (2.18–8.17 h), the volume of distribution at steady state (Vd_{ss}) (2.5–15.1·l/m^{-2}) and the systemic clearance (Cl_s) (10.1–35.1 ml min^{-1}·m^{-2}) with the resulting mean values and standard deviations were determined. Our findings are compared with those of other authors, especially with regard to the method of detection used. This comparison indicates similar individual deviations and shorter half-lives with increasing specificity of the employed assay. Four patients studied on 3 consecutive days and, in one instance, during two different cycles of chemotherapy showed no sign of accumulation or of accelerated excretion of etoposide. There was little intrapatient variability. The pharmacokinetic parameters were correlated to clinical and laboratory findings. Statistical analysis indicated that the AUC was increased by prior cisplatin therapy and in patients with elevated levels of alkaline phosphatase. The Cl_s was decreased by prior cisplatin therapy, in obese patients, and by elevated alkaline phosphatase. The t½β of etoposide was increased in older patients. Linear regression analysis yielded a grater Vd_{ss} in patients with lower serum albumin levels, but this correlation has not yet been found to be statistically significant.

Introduction

Etoposide is a semisynthetic derivative of podophyllotoxin, a mitotic inhibitor extracted from the root stock (rhizome) of the plant *Podophyllum peltatum.* The two compounds were first tested in humans in the early 1970s and have now become important antineoplastic agents. Although pharmacokinetic knowledge of both substances is limited, the available information reveals marked interpatient variability [1, 3, 5–8, 12–16, 18–21]. This suggests that therapeutic drug monitoring may play an important role in their clinical use.

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Prior to defining any crucial points of time and parameters relevant to therapy, however, the degree of variability, independent of analytical problems and procedures, must be evaluated. Although sensitive and quite specific detection methods combining high-performence liquid chromatography (HPLC) with either ultraviolet, fluorescence or electrochemical detection have recently been devised, the influence of patient-specific and biomedical variables upon pharmacokinetic parameters is still undetermined.

Recently, several studies relating to different aspects of etoposide pharmacokinetics have been published [1, 2, 4, 5, 8–11, 12–14, 17, 19–21]. Research dealing with the dose dependency of etoposide [8], the extent of penetration into cerebrospinal fluid [13, 17, 21], and tissue concentrations achieved under etoposide therapy [14, 21] document the interest this drug has generated among researchers and clinicians.

Two reports attempting to correlate clinical data to pharmacokinetic data were based upon small numbers of patients [2, 19]. They agree with regard to the distinct influences of creatinine clearance and of altered serum albumin concentrations [2, 19], but the influence of elevated serum glutamic pyruvate transaminase (GPT) levels and other liver function tests is still a matter of some controversy. Furthermore, one of the two groups [19] found a distinct correlation between prior cisplatin therapy and systemic and renal clearance of etoposide. Both studies fail to answer the question of whether dose reduction is madatory in patients with impaired hepatic and renal functions [2, 19]. Using a highly specific analytical procedure for the evaluation of etoposide plasma levels [4] the present study indicates shorter elimination half-lives of etoposide than most of the earlier investigations using other detection methods, and shows comparable intra- and interindividual variations of pharmacokinetic parameters. The report provides correlations between pharmacokinetic data and clinical and biochemical data. These were established in a larger number of patients and 24 h kinetic measurements.

Patients and methods

Fiften adult patients, 13 men and two women, were included in the study after giving informed consent. They ranged from 25 to 74 years of age, the median age being 60 years. All patients received polychemotherapy, and etoposide was administered on consecutive days as required.

Prior to parenteral application, the drug was dissolved in either 250 ml or 500 ml (0.9%) NaCl solution. In cases where the polychemotherapeutic regimen required different infusions per day, etoposide was administered as the first medication on the day of the study. Consecutive blood samples were drawn from a peripheral vein in 5-ml portions via an indwelling catheter, and each time the first portion of blood was discarded. The samples were collected in tubes containing sodium citrate, centrifuged, and the plasma obtained was frozen at −20° C for later assay. Samples were taken before and immediately after the infusion and subsequently at six to eight time points during a 24-h period, half of these during the first 4 h.

Table 1 lists the individual characteristics of patients included in this study and their clinical and biochemical properties, which were correlated to standard pharmacokinetic parameters. In addition to those mentioned in Table 1 the following values were established and correlated:

- Nutritional status, defined as a deviation from normal weight (body height in cm minus 100, expressed in kg).
- Toxic effect of chemotherapy (determined by the white blood cell count before and after chemotherapy).
- Serum levels of triglycerides and cholesterol.

When establishing correlations between clinical and biochemical values and pharmacokinetic parameters, patients who had received cisplatin therapy were excluded from calculations for single parameters if the cisplatin therapy was found to influence the parameter under investigation.

Etoposide assay. In all plasma samples etoposide concentrations were measured according to the method described in detail in the first part of this study [4].

Pharmacokinetic calculations. Pharmacokinetic parameters describing etoposide distribution were calculated from the serial plasma concentrations vs time data with the appropriate multiexponential equations. Graphical analysis indicated a biexponential fall in plasma concentration time data in all patients. A monoexponential decline was not observed. Accordingly, the postinfusion plasma drug concentrations were fitted to a biexponential equation.

Peak plasma levels were determined by collecting the first sample immediately after the infusion. The area under the plasma concentration curve (AUC) and the area under

Table 1. Demographic, biochemical, and clinical characteristics of the 15 patients

Patient	Diagnosis	Age (years)	Sex	Body surface area (m^2)	Therapy	Serum creatinine ($mg \cdot dl^{-1}$)	Cl_{cr} ($ml \cdot min^{-1}$)	Albumin ($gm \cdot dl^{-1}$)	SGPT ($U \cdot l^{-1}$)	Alkaline phosphatase ($U \cdot l^{-1}$)	γ-GT ($U \cdot l^{-1}$)	Total cisplatin ($mg \cdot m^{-2}$)[a]	Prior chemotherapy[b]
RE	SCLC	57	M	1.7	VP,I,O	1.1	40	4.0	5	86	10	ND	A,C,O, VP,I
JW	NHL	69	M	1.85	C,A,O, Pr,VP	1.0	ND	3.0	10	162	33	ND	A,C,O, Pr
PP	SCLC	72	M	1.88	VP,I,O	0.8	ND	2.9	6	109	12	ND	VP,I,O
TF	HD	39	F	1.36	CC,VP, O,D	0.8	ND	ND	23	941	354	ND	C,O,N, Pr,A,DI, CC,VP,D
MR	NHL	62	M	2.05	C,A,O, Pr,VP	0.9	ND	3.6	15	76	34	ND	A,C,O, Pr,VP
HP	MM	55	M	2.2	O,C,Pr, VP	1.1	100	3.1	6	98	12	ND	M,Pr,O, C,VP
VH	SCLC	61	M	1.8	VP,I,O	1.2	70	3.6	27	249	34	ND	ND
HK	SCLC	61	M	1.85	VP,I,O	1.2	54	3.6	6	172	19	ND	VP,I,O
KW	NSCLC	62	M	1.8	VP,Vd,P	1.1	70	3.8	45	165	26	100	P
HW	NHL	65	M	1.7	C,A,O, Pr,VP	1.0	ND	4.0	15	246	89	ND	C,A,O, Pr,VP
SchO	NHL	42	M	2.1	C,A,O, Pr,VP	1.0	ND	4.1	21	84	11	ND	C,A,O, Pr,VP
WM	NHL	66	F	1.7	C,A,O, Pr,VP	1.1	ND	ND	7	ND	–	ND	C,A,O, Pr,VP
BL	HNC	42	M	1.7	VP,Vd,P	0.9	91	3.8	3	ND	31	100	P
SchK	TT	25	M	2.15	B,P,VP	1.2	74	4.6	25	127	14	400	P,Vd,B
BO	GC	60	M	2.0	P,VP	1.1	54	3.4	13	125	12	ND	ND

SCLC, small cell lung cancer; NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease; MM, multiple myeloma; NSCLC, non-small cell lung cancer; HNC, head and neck cancer; TT, teratoma of the testis; GC, gastric cancer; Cl_{cr}, creatinine clearance; SGPT, serum glutamic pyruvate transaminase; GT, gamma-glutamyl transpeptidase; ND, no data

[a] Cumulative cisplatin dosage prior to etoposide pharmacokinetic study

[b] Chemotherapy received before etoposide pharmacokinetic study: A, adriamycin; B, bleomycin; C, cyclophosphamide; I, ifosfamide; O, oncovine; P, cisplatin; Pr, prednisone; D, dexamethasone; VP, etoposide; CC, cyclohexylchloroethylnitrosourea (CCNU); N, procarbazine; DI, dacarbazine; M, melphalane; Vd, vindesine; Vb, vinblastine

the moment curve (AUMC) were calculated by the trapezoidal method from zero to the last point of time measured, and from there to infinite time by first-order extrapolation using the $t_{1/2}\beta$ value of etoposide. Noncompartmental parameters, such as the systemic clearance (Cl_s) and the volume of distribution at steady state (Vd_{ss}), were computed using the following equations:

$$Cl_s = \frac{D}{AUC}$$

$$Vd_{ss} = Cl_s \left(\frac{AUMC}{AUC} - \frac{t'}{2} \right),$$

where D is dose and t' is infusion duration.

Statistical analysis. Student's two-way *t*-test was employed to determine whether the influence of clinical or laboratory data upon pharmacokinetic parameters was statistically significant. A *P* value of ≤ 0.05 was assumed to indicate a positive correlation.

Correlation coefficients were derived from linear regression analysis.

Results

Table 2 shows the pharmacokinetic data established in 15 patients using the procedure described above. Each patient is listed individually with the corresponding values. In cases where several kinetics were obtained from the same patient and/or different cycles of chemotherapy were monitored, mean values are given. In these instances standard deviations were computed and placed behind the mean value, thus indicating the extent of individual variability and allowing comparison with other authors and methods of detection.

The parameters range as follows: peak plasma level 9.5–63.3 $\mu g \cdot ml^{-1}$; AUC 2707–10192 $\mu g \cdot ml^{-1} \cdot min^{-1}$; mean transit time (MTT) 2.7–10.6 h; the elimination half-lives $t_{1/2}\alpha$ 0.10–0.52 h, $t_{1/2}\beta$ 2.18–8.17 h; Vd_{ss} 2.5–15.1 $l \cdot m^{-2}$; Cl_s 10.1–35.1 $ml \cdot min^{-1} \cdot m^{-2}$. This marked degree of interpatient deviation contrasts with a comparatively small degree of intrapatient variability as expressed by the moderate standard deviation (Table 2).

Table 3 is a chronological summary of pharmacokinetic parameters already published. As far as possible the age of the patients included in the study, the method of detection, and the dose of etoposide administered are stated. Standard deviations not supplied by the authors were calculated whenever individual values were available.

Table 4 groups the studies performed with adults according to the method used for the etoposide assay. The methods are listed according to increasing specificity. The mean values of given pharmacokinetic parameters for each detector were obtained by multiplying the mean value of a study by the number of patients included in it, adding up the results for each detection method, and dividing the total by the number of patients in the same group.

Fig. 1 shows the compartment-dependent parameters AUC and $t_{1/2}\beta$ and the compartment-independent parameter Cl_s as established on 3 consecutive days for four patients. Patient RE was monitored during two independent cycles of chemotherapy.

Individual clinical and demographic parameters of all patients included are summarized in Table 1. Creatinine clearance was estimated in eight patients and was found to be less than 60 ml/min in only three patients. Since all of these patients had a creatinine serum level within the normal range and no indication of renal disease, a urine collection error could not be ruled out. Some abnormal liver function tests were found in these patients. Eight of the 15 patients studied showed elevated levels in one or more of

Table 2. Pharmacokinetic parameters of 15 patients with various malignancies. Patient characteristics are given in Table 1

Patient	n/m[a]	Infusion time (infin.)	Dose ($mg \cdot m^{-2}$)	Peak level ($\mu g \cdot ml^{-1}$) (SD)	AUC ($\mu g \cdot ml^{-1} \cdot min^{-1}$) (SD)	MTT (h) (SD)	$t_{1/2}\alpha$ (h) (SD)	$t_{1/2}\beta$ (h) (SD)	Vd_{ss} ($l \cdot m^{-2}$) (SD)	Cl_s ($ml \cdot min^{-1} \cdot m^{-2}$) (SD)
	6/2	50–100	80	14.7	2707 (494)	4.72 (0.88)	0.37 (0.05)	4.18 (1.34)	7.66 (2.21)	31.1 (4.91)
JW	3/1	65–160	85	10.0	3007 (176)	6.72 (1.2)	0.24[b]	4.46 (0.1)	10.5 (1.04)	30.3 (2.1)
PP	3/1	28–80	105	15.43	4403 (1091)	10.6 (1.3)	0.39 (0.06)	8.17 (0.88)	15.1 (3.17)	25.1 (5.78)
TF	3/1	55–192	95	18.66	5806 (584)	6.13 (0.9)	0.32 (0.03)	3.94 (0.75)	5.3 (1.5)	16.5 (1.74)
MR	2/1	43±60	95	23.25	4374 (272)	5.5 (0.8)	0.29 (0.08)	4.31 (0.53)	6.6 (1.55)	21.2 (1.27)
HP	2/2	45±50	110	18.65	4756 (502)	5.9 (1.16)	0.10 (0.04)	4.07 (0.72)	7.5 (0.85)	23.05 (2.74)
VH	1/1	120	80	9.5	4573	8.1	ND	4.5	7.5	17.6
HK	1/1	20	80	44.0	2977	2.7	0.52	3.04	4.2	27.2
KW	1/1	55	100	37.3	9822	5.1	0.23	3.39	2.8	10.5
HW	1/1	105	120	16.0	5182	7.6	0.28	5.49	9.1	22.7
SchO	1/1	83	115	26.6	6663	4.47	0.28	3.0	3.9	17.1
WM	1/1	95	120	18.4	5693	5.27	ND	3.35	5.5	20.6
BL	1/1	40	100	63.3	8574	4.7	0.43	4.1	3.0	11.6
SchK	1/1	105	95	30	10192	6.0	ND	3.68	2.5	10.1
BO	1/1	80	100	17.6	2843	3.2	0.23	2.18	5.2	35.15
All patients	28/17	20–192	80–120	24.2 (14.4)	4667 (2144)	6.09 (2.1)	0.313[c] (0.106)	4.44 (1.6)	7.526 (3.73)	23.7 (7.66)

ND, no data

[a] n, number of 24 h kinetics of etoposide; m, number of cycles of polychemotherapy

[b] Present only in one 24 h kinetic

[c] Number of kinetics = 21

Table 3. Review of pharmocokinetic parameters published in the literature

Number of patients	Age (years)	Number of kinetics	Methods	$t_{1/2}\alpha$ (h) (SD)	$t_{1/2}\beta$ (h) (SD)	AUC ($\mu g \cdot ml^{-1} \cdot min^{-2}$) (SD)	Cl_s ($ml \cdot min^{-1} \cdot m^{-2}$) (SD)	Vdl_{ss} ($l \cdot m^{-2}$) (SD)	MTT (h) (SD)	Reference year	Dose ($mg \cdot m^{-2}$)
11	ND	11	^3H	0.59 (0.64)	6.66	ND	27.1 (12.5)	10.6 (3.2)	ND	[1] 1975	130–290
7	ND	7	^3H	0.89 (1.07)	20.2	2218 (827)	ND	ND	ND	[16] 1978	130–290
2	ND	2	HPLC-UV	ND	4.5 (0.7)	ND	ND	ND	ND	[7] 1981	100
14	12–55	14	HPLC-UV	1.18 (0.54)	7.05 (2.5)	4580 (2568)	26.8 (9.0)	15.7 (6.84)	ND	[13] 1982	100[a]
6	3.7–9.5	7	HPLC-UV	0.58 (0.46)	3.37 (1.44)	5200 (3474)	39.3 (17.4)	9.97 (2.58)	ND	[12] 1982	100
9	3–18	9	HPLC-EC	1.2 (1.7)	5.8 (3.2)	ND	17.8 (11.2)	4.87 (2.8)	ND	[5] 1982	200–250
2	ND	5	HPLC-EC	ND	10.16 (4.6)	ND	ND	ND	ND	[11] 1983	120
9	ND	9	HPLC-EC	0.5 (0.51)	4.1 (3.18)	6900 (2981)	ND	7.9 (3.05)	ND	[21] 1984	50–100
8	4–22	12	HPLC-EC	ND	6.5 (1.6)	ND	20.9 (5.4)	7.2 (1.7)	7.8 (1.9)	[19] 1984	200
12	65	12	HPLC-UV	0.79 (0.58)	8.05 (4.3)	22185 (45119)	28.0 (9.7)	25.2[b] (10.5)	ND	[8] 1984	400–800

If possible a lacking SD was calculated according to the reported values. Values were converted to uniform dimensions in any possible case

^3H, tritium labeling; HPLC, high-performance liquid chromatography; UV, ultraviolet detector; EC, electrochemical detector

[a] One patient 200 $mg \cdot m^{-2}$

[b] Given in liters

Table 4. Pharmacokinetic parameters of etoposide determined by different methods. The given mean values are weighted by the number of patients, included in each study

Detection method	Number of patients	$t_{1/2}\alpha$ (h)	$t_{1/2}\beta$ (h)	MTT (h)	Cl_s ($ml \cdot min^{-1} \cdot m^{-2}$)	Vd_{ss} ($l \cdot m^{-2}$)	Reference
^3H-label	18	0.71 n = 18	11.9 n = 18	ND	27.1 n = 11	10.6 n = 11	[1, 16]
HPLC-UV	28[a]	1.0 n = 26	7.3 n = 28	ND	27.3 n = 26	15.7 n = 14	[7, 8, 12]
HPLC-EC	28[b]	0.87 n = 27	6.26 n = 30	7.8 n = 8	19.26 n = 17	6.56 n = 25	[5, 11, 18, 20]
HPLC-MS	15	0.313 n = 21	4.4 n = 28	6.09 n = 28	23.7 n = 28	7.526 n = 28	Present study

HPLC, high-performance liquid chromatography; UV, ultraviolet; EC, electrochemical detector; MS, mass spectrometry; n, number of 24 h kinetics of etoposide; ND, no data

[a] Only adults are included

[b] This group includes children and adults, because authors did not supply detailed information regarding individual parameters and/or patient characteristics

the following biochemical parameters: Alkaline phosphatase (normal up to 180 $U \cdot l^{-1}$), GPT (normal up to 22 $U \cdot l^{-1}$), and gamma-glutamyl transpeptidase (γ-GT; normal up to 28 $U \cdot l^{-1}$). The total serum bilirubin was found to be in the normal range in all patients. One patient (VH) in the study had both bone metastasis and liver disease with an alkaline phosphatase level of 249 $U \cdot l^{-1}$. This elevated level may have been partly or completely due to the bone metastasis. Serum albumin ranged from 2.9 to 4.6 $g \cdot dl^{-1}$. Nutritional status, as shown in percent deviation from normal weight, ranged from −22% to +33%. The toxic effect of polychemotherapy was estimated on the basis of the peripheral platelet and white blood count (WBC) before the subsequent course of therapy. The values determined were normal in nearly all patients, five having values in the lower normal range. One male had only $2200 \cdot mm^{-3}$ leukocytes with a normal platelet count. The nadir was determined in three patients with a WBC be-

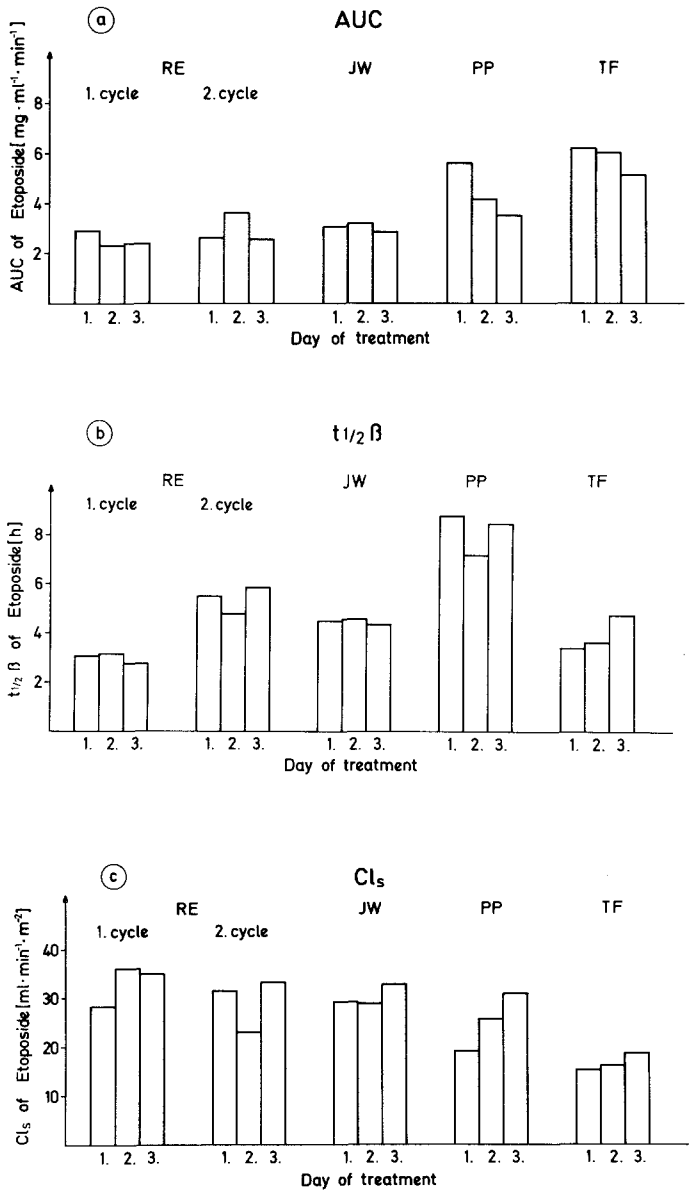

Fig. 1a–c. Pharmacokinetic parameters AUC **(a)** t½β **(b)**, and Cl_s **(c)** as established on 3 consecutive days for four patients

tween 1000 and 1200 · mm^{-3} and a corresponding platelet count ranging from 19000 to 120000 · mm^{-3}. Serum levels of cholesterol and triglycerides were included in the study due to the lipophilic properties of etoposide and in order to register any possible interaction that might influence pharmacokinetic values or analytical procedures. Five of the 15 patients studied had raised levels in one or both tests.

Analysis of the serum concentration vs time graphs indicated a biexponential decline in all patients, and these data were adequately described by the equation for a two-compartment open model. The Cl_s values computed with compartmental and with noncompartmental methods were not significantly different. The pharmacokinetic parameters for etoposide disposition determined from all 28 of the 24-h kinetics are summarized in Table 5.

Each of the pharmacokinetic parameters established was examined with regard to a possible correlation to the

Table 5. Pharmacokinetic parameters following 28 i.v. administrations of etoposide in 15 adult patients receiving polychemotherapy (mean ± SD)

Serum peak level	(μg · l^{-1})	24.2 ±14.4
AUC	(μg · ml^{-1} · min^{-1})	4667±2144
$t_{1/2}\alpha$	(h)	0.31± 0.11
$t_{1/2}\beta$	(h)	4.44± 1.6
MTT	(h)	6.1 ± 2.1
Vd_{ss}	(l · m^{-2})	7.5 ± 3.7
Cl_s	(ml · min^{-1} · m^{-2})	23.7 ± 7.7

Table 6. Overview of influence of patient-specific clinical and biochemical variables on pharmacokinetic parameters of etoposide

	AUC	Cl_s	Vd_{ss}	$t_{1/2}\beta$	MTT
SGPT	O	*↓	O	O	O
Alkaline phosphatase	*↑	+↓	O	O	*↑
γ-GT	O	*↓	O	O	O
Cholesterin	*↑	O	O	O	O
Triglyceride	*↑	O	O	O	O
Albumin	O	*↓	*↓	O	*↓
Age	O	O	+↑	+↑	*↑
Nutritional status	O	+↓	+↓	*↓	O
Prior cisplatin	+↑	+↓	+↓	O	O
Ifosfamide	O	O	O	O	O
Cyclophosphamide	O	O	O	O	O
Adriamycin	O	O	O	O	O
Creatinine clearance	O	O	O	O	O
Toxic effect of chemotherapy	O	O	O	O	O

+, significant influence; *, marked but not significant influence; O, no influence; ↑, parallel relationship; ↓, inverse relationship

clinical and biochemical values included in the study. An exception was the t½α of etoposide; since it was inconstant due to different durations of infusion, the group of patients that displayed a t½α was too small to allow a statistical evaluation.

The results of the statistical analysis are shown in Table 6. The linear regression diagrams and additional figures (Figs. 2–4) emphasize significant findings.

Discussion

Using a highly specific detector system the pharmacokinetic parameters of etoposide were established in 15 patients receiving polychemotherapy. In six patients more than one 24-h kinetic of this compound was obtained on consecutive treatment days. The mass spectrometer-based evaluation is associated with the shortest t½β (Tables 3, 4).

We understand this to be a result of the specificity of the mass spectrometric assay method. With increasing specificity of the detection method the etoposide t½β can be seen to become shorter (Table 4). The mean values of model-independent parameters (Cl_s and Vd_{ss}) are comparable to the results found with the relatively specific electrochemical detector system and differ more markedly from the values measured with the other detection systems. The t½α differs from the other parameters in being inconstant, proving to be undetectable in three patients (Table 2). This may be due to a relatively long infusion interval in these cases.

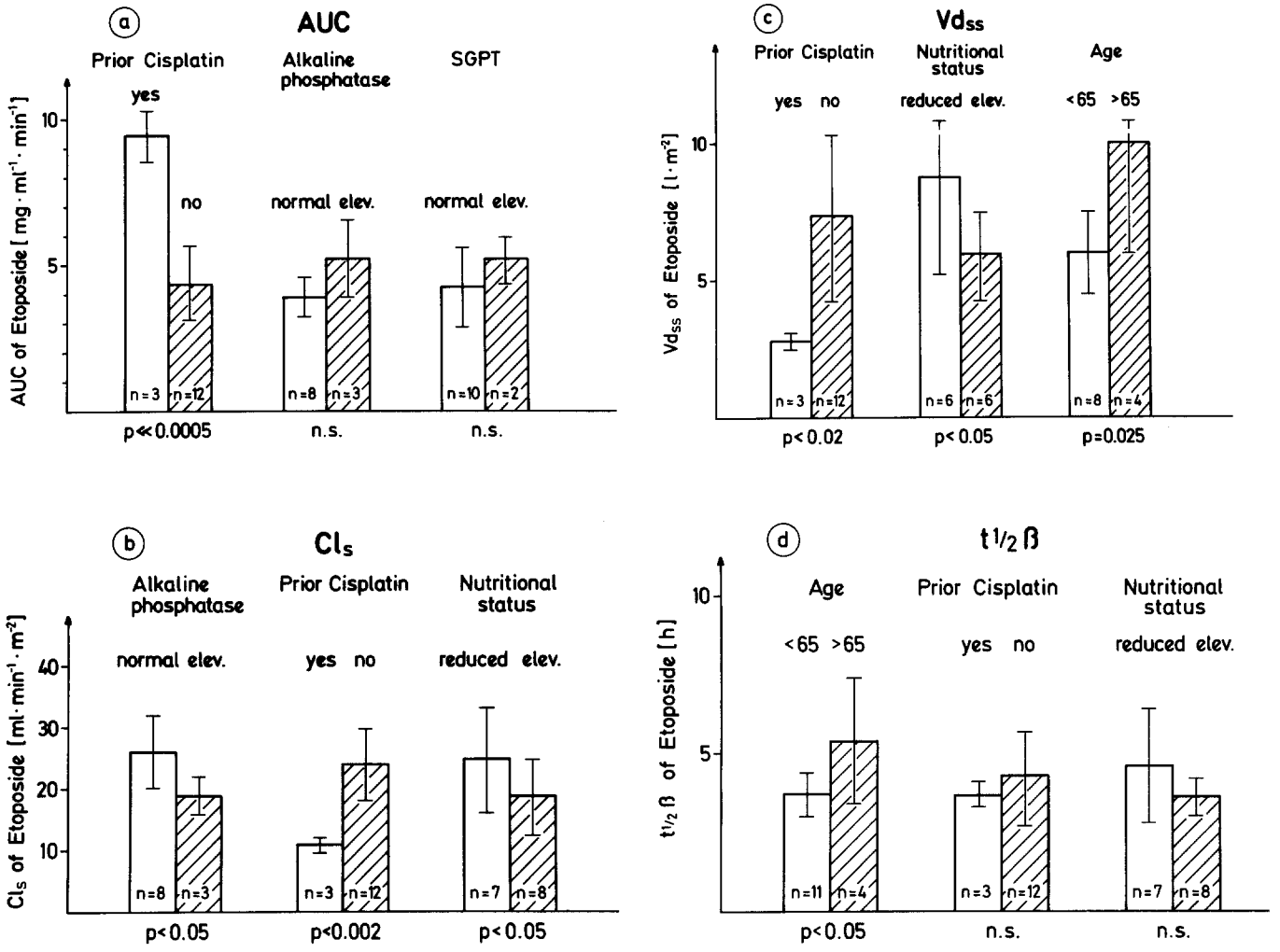

Fig. 2a–d. Influence of single clinical parameters on AUC **(a)**, Cl_s **(b)**, Vd_{ss} **(c)**, and $t^1/2\beta$ **(d)**. The values of Auc are normalized to a dose of 100 mg etoposide per m^2

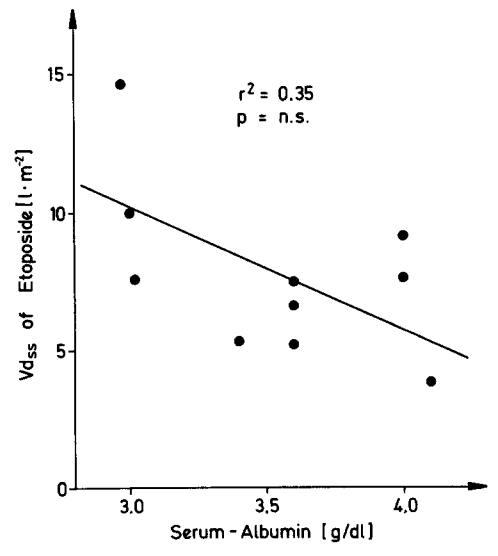

Fig. 3. Linear regression analysis of Vd_{ss} against serum albumin without two patients whose serum albumin was not determined (WM and TF) and the three patients who received prior cisplatin

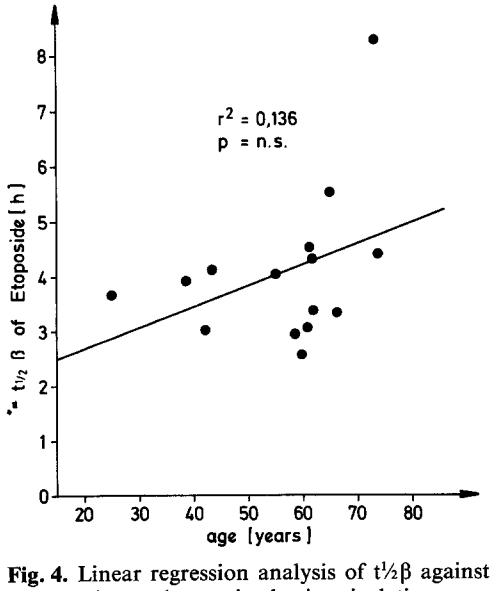

Fig. 4. Linear regression analysis of $t^1/2\beta$ against age without the three patients who received prior cisplatin

With regard to intrapatient and interpatient variability, our findings (Fig. 1, Table 2) are in agreement with other publications (Table 3).

Considering methodical and individual deviations, these results show no indication of either accumulation or accelerated elimination of etoposide in circumstances of simultaneous application of other antineoplastic drugs and supportive medications. This holds true for all the pharmacokinetic parameters determined.

Correlation of pharmacokinetic parameters of etoposide to clinical and biochemical characteristics revealed several interesting influences, some of which are statistically significant. Prior treatment with cisplatin was seen to have the most striking influence on AUC, Cl_s, and Vd_{ss}. As indicated in Table 6 and Fig. 2, all these pharmacokinetic parameters were significantly altered by prior cisplatin treatment.

Three patients received cisplatin 2 days prior to the etoposide application in the same polychemotherapy cycle. One further patient (BO in Table 2) received this drug on the same day after administration of etoposide. He showed an etoposide disposition comparable to that of the group of patients who had never received cisplatin. The MTT, the single distribution-elimination rate parameter that describes the average time a drug spends in the patient, and the model-dependent paramter $t\frac{1}{2}\beta$ were both not significantly altered in the subgroup of patients who had prior cisplatin. Sinkule et al. [19] reported lower systemic and renal clearances and longer $t\frac{1}{2}\beta$ and MTT in three patients after cisplatin. Arbuck et al. [2] evaluated pharmacokinetic parameters in 10 patients with etoposide and cisplatin application. They reported values of Cl_s and Vd_{ss} comparable to those determined in the subgroup of our patients who had never been treated with cisplatin, but there is no information available as to whether cisplatin was given before or after etoposide. Sinkule et al. [19] discussed an influence of prior cisplatin treatment on renal and hepatic function and its involvement in a decreased etoposide clearance. However, the present data indicate a marked increase of AUC and a decrease of Vd_{ss} with decreased Cl_s. These results indicate a change in the distribution pattern of etoposide following application of cisplatin. This interpretation is supported by the data from the patient BO, who received cisplatin on the same day but after termination of etoposide infusion. Interestingly, a higher toxicity of polychemotherapy in this subgroup of patients could not be observed. The exact mechanism is still to be elucidated.

Furthermore, AUC seems to be higher in patients with elevated levels of alkaline phosphatase and serum lipids. These preliminary data are not yet statistically significant, possibly due to the low numbers of patients involved. These trends have to be confirmed in further studies. With the exception of the relationship between alkaline phosphatase and Cl_s the same restriction holds true for the correlations between liver function tests (serum GPT, alkaline phosphatase, γ-GT in Table 6 and Fig. 2b) and serum albumin and CL_s, which is decreased by all these parameters. Similar influences were reported by Sinkule et al. [19] and Arbuck et al. [2], indicating a possible influence of altered liver function and plasma protein binding on etoposide disposition. There is a significant relationship between an improved nutritional status and a decreased Cl_s (Fig. 2b). This is concordant with a shorter $t\frac{1}{2}\beta$ (Fig. 2d) not being statistically proven.

The relationship of Vd_{ss} to clinical parameters is illustrated in Table 6 and Figs. 2c, and 4. In addition to the above-mentioned influence of prior cisplatin, the volume of distribution is significantly lower in patients with elevated body weight (Fig. 2c) and significantly higher in older patients (Fig. 4). To date these correlations have not been described for etoposide. In 1984 Sinkule et al. [18] reported, for the congener VM26, an inverse relationship between body weight and Vd_{ss}.

Serum albumin was reported to have an inverse relationship to renal clearance of etoposide [19]. This was said to be caused by the extensive binding of this compound to plasma proteins [1]. As shown in Fig. 3 and Table 6, elevated serum albumin lowers both Vd_{ss} and Cl_s. These findings are not yet statistically significant, but can also both be explained by the high ratio of protein-bound drug. The lower MTT in patients with elevated serum albumin (Table 6) is consistent with this hypothetical mechanism.

Furthermore, MTT and $t\frac{1}{2}\beta$ are found to be higher in older patients. In the case of $t\frac{1}{2}\beta$ (Fig. 2d), this relationship is already statistically significant, whereas for MTT (Table 6) this is not yet the case.

In summary, the present study has elucidated the importance of a highly specific analysis of etoposide for the evaluation of absolute values of pharmacokinetic parameters. Interindividual variations in the pharmacokinetic disposition of this compound resemble data reported in the relevant literature, so these variations may be independent of the detector system used. After repeated doses of etoposide no alterations in pharmacokinetic parameters could be observed. Intraindividual variations were found to be relatively small.

The analysis of possible relationships between the pharmacokinetic parameters of etoposide and patient-specific demographic, biochemical, and clinical conditions shows a unexpectedly high incidence of distinct correlations. Some of these influences are already statistically significant. This is particularly surprising in view of the small number of patients studied. Some further findings indicate distinct trends which are not yet statistically significant but which, in most cases, are consistent with correlations and trends reported by other investigators [2, 19]. These preliminary results compel oncologists and pharmacologists to perform further studies to elucidate the interactions of patient-specific parameters with etoposide disposition and to reveal the underlying mechanisms. The possibility of controlling these influences by establishing guidelines for individual dosage modifications and by simplified drug monitoring will result in more effective treatment of cancer patients.

References

1. Allen LM, Creaven PJ (1975) Comparison of the human pharmacokinetics of VM26 and VP16, two antineoplastic epipodophyllotoxin glucopyranoside derivatives. Eur J Cancer 11: 697
2. Arbuck SG, Douglas HO, Goodwin P, Nava H, Clark J, Crom WR, Evans WE (1985) Pharmacokinetics of etoposide (VP) in patients with normal and abnormal liver function. Proc ASCO 4: 40
3. Creaven PJ (1982) The clinical pharmacology of VM26 and VP16-213. A brief overview. Cancer Chemother Pharmacol 7: 133

4. Danigel H, Pflüger KH, Jungclas H, Schmidt L, Dellbrügge J (1985) Drug monitoring of etoposide (VP16–213). I. A combined method of liquid chromatography and mass spectrometry. Cancer Chemother Pharmacol 15: 121
5. Evans WE, Sinkule JA, Crom WR, Dow L, Look AT, Rivera G (1982) Pharmacokinetics of teniposide (VM26) and etoposide (VP16–213) in children with cancer. Cancer Chemother Pharmacol 7: 147
6. Evans WE, Sinkule JA, Crom WR, Dow L, Look T, Horvath A, Tivera G (1982) Pharmacokinetics of etoposide (VP16) in children with leukemia. Chemioterapia 1: 2
7. Farina P, Marzillo G, D'Incalci M (1981) High-performance liquid chromatography determination of VP16–213 in human plasma. J Chromatogr 222: 141
8. Hande KR, Wedlund PJ, Noone RM, Wilkinson GR, Greco FA, Wolff SN (1984) Pharmacokinetics of high-dose etoposide (VP16–213) administered to cancer patients. Cancer Res 44: 379
9. Harvey VJ, Slevin ML, Joel SP, Johnston A, Wrigley PFM (1985) The effect of food and concurrent chemotherapy on the bioavailability of oral etoposide. Br J Cancer 52: 363
10. Harvey VJ, Slevin ML, Joel SP, Smythe MM, Johnston A, Wrigley PFM (1985) Variable bioavailability following repeated oral doses of etoposide. Eur J Cancer Clin Oncol 21: 1315
11. Holthuis JJM, Römkens FMGM, Pinedo HM, Oort WJ van (1983) Plasma assay of the antineoplastic agent VP16–213 (etoposide) using high-performance liquid chromatography with electrochemical detection. J Pharmaceut Biomed Anal 1: 89
12. D'Incalci M, Farina P, Sessa C, Mangioni C, Conter V, Masera G, Rocchetti M, Pisioni MB, Piazza E, Beer M, Cavalli F (1982) Pharmacokinetics of VP16–213 given by different administration methods. Cancer Chemother Pharmacol 7: 141
13. D'Incalci M, Farina P, Sessa C, Molina P, Mangioni C, Jancovich M, Masera G, Beer M, Cavalli F (1982) Pharmacokinetic of VP16 in humans. Chemoterapia 1: 2
14. D'Incalci M, Sessa C, Rossi C, Roviaro G, Mangioni C (1985) Pharmacokinetics of etoposide in gestochoriocarcinoma. Cancer Treat Rep 69: 69
15. D'Incalci M, Rossi C, Sessa C, Urso R, Zucchetti M, Farina P, Mangioni C (1985) Pharmacokinetics of teniposide in patients with ovarian cancer. Cancer Treat Rep 69: 73
16. Pelsor FR, Allen LM, Creaven PJ (1978) Multicompartment pharmacokinetic model of 4'-demethylepipodophyllotoxin 9-(4,6-*O*-ethylidene-β-*D*-glucopyranoside) in humans. J Pharmaceut Sci 67: 1108
17. Postmus PE, Holthuis JJM, Haaxma-Reiche H, Mulder NH, Vencken LM, van Oort WJ, Sleijfer DT, Sluiter HJ (1984) Penetration of VP16-213 into Cerebrospinal Fluid After High-Dose Intravenous Administration. J Clin Oncol 2: 215
18. Sinkule JA, Stewart CF, Crom WR, Melton ET, Dahl GV, Evans WE (1984) Teniposide (VM26) disposition in children with leukemia. Cancer Res 44: 1235
19. Sinkule JA, Hutson P, Hayes FA, Etcubanas E, Evans W (1984) Pharmacokinetics of etoposide (VP16) in children and adolescents with refractory solid tumors. Cancer Res 44: 3109
20. Smyth RD, Pfeffer M, Scalzo A, Comis RL (1985) Biovailability and pharmacokinetics of etoposide (VP16). Sem Oncol XII: 48
21. Stewart DJ, Richard MT, Hugenholtz H, Dennery JM, Belanger R, Gerin-Lajoie J, Montpetit V, Nundy D, Prior J, Hopkins HS (1984) Penetration of VP16 (etoposide) into human intracerebral tumors. J Neuro-Oncol 2: 133

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