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Pharmacokinetics of etoposide: correlation of pharmacokinetic parameters with clinical conditions

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Summary. The pharmacokinetic parameters of etoposide were established in 35 patients receiving the drug parenterally within the framework of different polychemotherapy protocols. A total of 62 data for 24-h kinetics were analysed. After sample extraction and high-performance liquid chromatography (HPLC) or thin-layer cromatographic (TLC) separation, etoposide was measured by means of [^{252}Cf]-plasma desorption mass spectrometry (PDMS). This highly specific detection system proved to be very practicable and reproducible. The present study comprised two parts that were absolutely comparable in terms of clinical and pharmacokinetic parameters. In part II of the study, sensitivity was improved by modifying the analytical technique. After the exclusion of patients who had previously been given cisplatin or who exhibited renal impairment and of one patient who showed extremely high levels of alkaline phosphatase, γ-GT and SGPT, the mean values calculated for the pharmacokinetic parameters evaluated were: beta-elimination half-life ($t_{1/2\beta}$), 4.9 ± 1.2 h; mean residence time (MRT), 6.7 ± 1.4 h; area under the concentration-time curve (AUC), 5.43 ± 1.74 mg min ml^{-1}; volume of distribution at steady state (Vd_{ss}), 6.8 ± 2.7 l/m^2; and clearance (Cl), 18.8 ± 5.3 ml min^{-1} m^{-2}. The pharmacokinetic parameters were correlated with 12 different demographic or biochemical conditions. Impaired renal function, previous application of cisplatin and the age of patients were found to influence etoposide disposition to a statistically significant extent. We suggest that the dose of etoposide should be reduced in elderly patients and/or in individuals with impaired renal function, especially in those exhibiting general risk factors such as reduced liver function with regard to the polychemotherapy.

Introduction

In the present study we sought to establish the pharmacokinetics of several antitumour drugs in clinical use. Two of the commonly used cytotoxic drugs are the epipodophyllotoxin derivatives etoposide (VP 16-213) and teniposide (VM 26), both of which are active against a number of human malignant diseases. Etoposide was introduced into clinical trials in the early 1970s and has since been established in the treatment of several malignancies, including small-cell lung cancer, germ-cell tumours, leukaemia and lymphomas. However, knowledge of the pharmacokinetics of either substance remains limited, and the information available reveals marked interindividual variability [1, 3, 6–8, 10–12, 14, 19, 21–24]. The detection of pharmaceuticals in biological fluids such as blood and urine requires careful sample preparation and a sensitive and specifically devised detection technique. Liquid chromatography (LC) provides a reasonable method of cleaning up the sample after extraction.

For quantitative analyses a fluorescence, UV-absorption or electrochemical detector is commonly used in LC, but mass spectrometry constitutes a more specific technique. In the present study we made use of [^{252}Cf]-plasma desorption mass spectrometry (PDMS) as a specific detector of non-volatile and thermally unstable molecules.

In part I of this study [20], pharmacokinetic parameters of etoposide were determined in 15 patients with various malignancies and were correlated with the patients' clinical, demographic and biochemical characteristics. We detected individual deviations similar to those found by other

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Table 1. Demographic and clinical parameters from the two parts of the study

Patient	Sex (M/F)	Body surface area (m^2)	Age (years)	(Poly)chemotherapy	Serum creatinine (mg/dl)	Creatinine clearance (ml/min)	Serum protein (mg/dl)	SGPT (units/l)	Alkaline phosphatase (units/l)	γ-GT (units/l)
Part I:										
R. E.	M	1.70	57	VP/I/O	1.10	40	6.60	5	86	10
J. W.	M	1.85	69	VP/Pr/C/A/O	1.00		5.00	10	162	33
P. P.	M	1.88	72	VP/I/O	0.80		4.80	6	109	12
T. F.	F	1.36	39	VP/CC/O/D	0.80			23	941	354
M. R.	M	2.05	62	VP/Pr/C/A/O	0.90		6.00	15	76	34
H. P.1	M	2.20	55	VP/Pr/O/C	1.10	100	5.20	6	98	12
V. H.	M	1.80	61	VP/I/O	1.20	70	6.00	27	249	34
H. K.	M	1.85	61	VP/I/O	1.20	54	6.00	6	172	19
K. W.	M	1.80	62	VP/Pl/Vd	1.10	70	6.30	45	165	26
H. W.	M	1.70	65	VP/Pr/C/A/O	1.00		6.70	15	246	89
Sch. O.	M	2.10	42	VP/Pr/C/A/O	1.00		6.80	21	84	11
W. M.	F	1.70	66	VP/Pr/C/A/O	1.10			7		
B. L.	M	1.70	42	VP/Pl/Vd	0.90	91	6.30	3		31
Sch. K.	M	2.15	25	VP/Pl/B	1.20	74	7.70	25	127	14
B. O.	M	2.00	60	VP/Pl	1.10	54	3.40	13	125	12
Part II:										
M. C.	F	1.90	48	VP/Pl	0.80	112	6.50	6	156	22
O. C.	M	1.50	55	VP	0.80		6.60	13	113	25
M. D.	F	1.60	72	VP/Vd/C/A	0.60	84	6.80	12	116	16
E. F.	M	1.90	51	VP/C/A	0.70	128	7.50	13	348	
F. F.	M	1.80	65	VP/I	0.80	71	5.80		135	29
N. G.	M	1.90	38	VP/Pl/Vd	1.10	106	6.80	39	88	18
G. H.1	M	1.80	50	VP/I	0.80	100	6.50		86	12
G. H.2	M	1.80	51	VP	0.80	95	7.20	10	88	8
G. H.3	M	1.70	51	VP/Pl	0.60	120	7.50	5	100	12
J. H.	M	1.90	67	VP/Pl	1.10		7.00	15	116	26
G. K.	M	1.90	23	VP/Vd/C/A	1.30	113	7.40	22	153	55
R. L.	M	1.50	47	VP	2.10	39	6.40	11	159	
K. M.	F	1.50	64	VP/Vd/C/A	0.90		5.00	39	1,705	298
A. M.	M	1.90	64	VP/I	2.20	24	6.00	8	220	49
H. M.	M	1.60	51	VP/Pl/Vd	0.90	63	7.40	18	139	
J. N.	M	1.70	74	VP/Vd/C/A	1.10	35	6.10	4	106	
H. P.2	M	2.00	57	VP/Vd/C/A	0.80	112	6.20	7	148	18
R. S.	M	1.80	56	VP/I	0.70	98	6.70	14	117	38
K. S.	M	1.70	71	VP/Vd/C/A	2.70	12	6.20	17	160	63
H. S.	M	1.90	45	VP	0.80	108	7.10	18	78	22

A, adriamycin; B, bleomycin; C, cyclophosphamide; CC, lomustine; D, dexamethasone; I, ifosfamide; O, oncovine; Pl, cisplatin; Pr, prednisone; Vd, vindesine; VP, etoposide; SGPT, serum glutamic pyruvate transaminase; γ-GT, gamma-glutamyl transpeptidase

authors but also noted markedly shorter half-lives for etoposide, which were attributable to the increased specificity of the method employed. The statistical analysis indicated an influence of previous application of cisplatinum, age and alkaline phosphatase and serum albumin levels on the pharmacokinetic parameters. To verify these initial results, we analysed 34 data for 24-h kinetics obtained in 20 further patients in part II of the study. The results obtained in the two parts of the investigation are summarised herein. Part I comprises detailed information on 15 patients and a total of 28 data for 24-h kinetics [20]. Thus, this study contains information on 35 patients and 62 data for 24-h kinetics demonstrating correlations between the pharmacokinetic parameters of etoposide and clinical as well as biochemical conditions.

Patients and methods

Patients. After the comparability of the two groups had been tested by the chi-square test, all 35 patients were fitted into a single group with homogeneous clinical, demographic and biochemical parameters. The 31 men and 4 women with histologically confirmed diagnoses who had given their informed consent to participate in the study included those with bronchial carcinoma (15 patients), non-Hodgkin's lymphoma comprising multiple myeloma (14 patients), head and neck cancer (3 patients), testicular cancer (1 patient), Hodgkin's disease (1 patient) and gastric cancer (1 patient). Except 3 patients all received polychemotherapy, and etoposide was given on 3 consecutive days. The age of the patients ranged from 23 to 74 years. Before polychemotherapy was started, their 24-h creatinine clearance was measured. Individual demographic and biochemical characteristics of the 35 patients, including 15 patients investigated in part I and 20 patients evaluated in part II, are summarised in Table 1 and their pharmacokinetic parameters are given in Table 2.

Treatment and sample collection. Prior to parenteral application, the drug was dissolved in either 250 or 500 ml (0.9%) NaCl solution. In cases in

Table 2. Pharmacokinetic parameters from the two parts of the study

Patients	Dose (mg/m^2)	Cisplatin dose (mg/m^2)	Infusion time (min)	Peak level (μg/ml)	AUC (μg min ml^{-1})	MRT (h)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	Vd_{ss} (l/m^2)	Cl (ml $min^{-1}m^{-2}$)
Part I:										
R. E.	80		75	14.70	2,707	4.72	0.37	4.18	7.66	31.10
J. W.	85		85	10.00	3,007	6.72	0.24	4.46	10.50	30.30
P. P.	105		50	15.43	4,403	10.60	0.39	8.17	15.10	25.10
T. F.	95		75	18.66	5,806	6.13	0.32	3.94	5.30	16.50
M. R.	95		60	23.25	4,374	5.50	0.29	4.31	6.60	21.20
H. P.1	110		50	18.65	4,756	5.90	0.10	4.07	7.50	23.05
V. H.	80		120	9.50	4,573	8.10		4.50	7.50	17.60
H. K.	80		20	44.00	2,977	2.70	0.52	3.04	4.20	27.20
K. W.	100	100	55	37.30	9,822	5.10	0.23	3.39	2.80	10.50
H. W.	120		105	16.00	5,182	7.60	0.28	5.49	9.10	22.70
Sch. O.	115		83	26.60	6,663	4.47	0.28	3.00	3.90	17.10
W. M.	120		95	18.40	5,693	5.27		3.35	5.50	20.60
B. L.	100	100	40	63.30	8,574	4.70	0.43	4.10	3.00	11.60
Sch. K.	95	400	105	30.00	10,192	6.00		3.68	2.50	10.10
B. O.	100	no data	80	17.60	2,843	3.20	0.23	2.18	5.20	35.15
Part II:										
M. C.	120	150	97	21.00	6,007	7.70	0.45	4.80	6.00	16.00
O. C.	250		152	36.50	5,326	7.00	0.91	5.80	7.40	19.10
M. D.	100		75	12.80	3,593	6.90	0.57	5.20	7.00	17.00
E. F.	100		55	17.80	4,122	4.90	0.40	3.60	6.60	23.50
F. F.	120		34	23.00	6,250	8.70	0.33	6.30	7.50	14.90
N. G.	100	190	133	25.10	7,504	6.80	0.45	5.80	4.80	13.80
G. H.1	120		81	24.00	3,512	4.80	0.80	4.40	9.20	26.50
G. H.2	250		114	36.00	4,967	9.60	0.90	8.20	5.90	19.10
G. H.3	120	140	92	17.10	3,979	6.70	0.11	5.80	8.80	24.50
J. H.	120	180	125	14.00	4,790	7.60	0.38	4.80	4.30	10.60
G. K.	100		34	23.70	4,333	4.50	0.46	3.90	5.90	23.90
R. L.	120		64	28.00	7,383	6.80	0.79	5.50	5.50	13.50
K. M.	100		21	17.30	3,081	10.80	0.60	11.10	20.60	32.00
A. M.	100		101	25.80	12,049	10.70	0.74	7.70	4.90	8.30
H. M.	100	150	102	23.50	9,649	9.20	0.40	6.60	5.00	9.90
J. N.	100		38	27.00	6,546	6.50	0.90	5.50	5.50	14.80
H. P.2	100		43	18.70	4,758	6.70	0.73	5.20	7.80	20.40
R. S.	120		80	23.30	4,419	5.20	0.69	4.20	5.70	21.00
K. S.	100		52	28.00	10,278	7.50	0.40	5.40	4.10	9.70
H. S.	100		131	24.60	4,256	6.40	0.43	6.40	5.90	21.40

AUC (values were normalized to a dose of 100 mg/m^2), Area under the concentration-time curve; MRT, Mean residence time; $t_{1/2\alpha,\beta}$, elimination half-life during the alpha and beta phases; Vd_{ss}, volume of distribution at steady state; Cl, clearance

which the polychemotherapeutic protocol required a number of different infusions on a particular day, etoposide was given as the first medication. Consecutive blood samples were drawn from a peripheral vein in 5-ml portions via an indwelling catheter, and the first portion of blood was discarded each time. The samples were collected into tubes containing sodium citrate and were subsequently centrifuged. The plasma obtained was frozen at –20° C. Samples were taken prior to and immediately following the infusion as well as six to eight times subsequently during a 24-h period, half of these being obtained during the first 4-h interval.

Etoposide assay. In all plasma samples of the first 15 patients in whom 28 data for 24-h kinetics were obtained etoposide concentrations were measured according to the method previously described in detail elsewhere [4, 5, 15, 16]. The etoposide analysis involving the 20 patients participating in part II of the present study was performed in 4 stages: sample extraction, sample purification by thin-layer chromatography (TLC), target preparation and quantitative sample detection by [^{252}Cf]-PDMS. The quantitative result is obtained by comparing the two mass lines corresponding to the two molecular ions of etoposide at m/z 588 and of the internal standard teniposide at m/z 656. The feasibility of the method was tested by varying the concentration ratio of etoposide/teniposide in blank serum samples over 4 orders of magnitude. The calibration curves for the analytical method used in part I [high-performance liquid chromatography (HPLC)/PDMS] and for the techniques applied in part II (TLC/PDMS) are linear and reproducible; however, the new TLC/PDMS assay achieves a lower detection limit of 50 ng/ml [17]. In clinical use, the etoposide concentration (24-h kinetics) was much higher than the detection limit of both analytical methods; therefore, the analytical techniques used in both parts of the study proved to be practicable and reproducible.

Pharmacokinetic calculations. The pharmacokinetic parameters describing etoposide distribution were calculated from serial plasma concentration versus time data using appropriate multiexponential equations. Graphical analysis indicated a biexponential decrease in the plasma concentration versus time data for all patients. A monoexponential decline was not observed. Accordingly, the post-infusion plasma drug concentrations were fitted to a biexponential curve. The pharmacokinetic parameters were calculated by the methods used in part I of this study [20].

Statistical analysis. The chi-square test, multivariate correlation analysis and Mann-Whitney's *U*-test were employed to determine whether the

Table 3. Mean values for all parameters evaluated in the two parts of the study

Parameter	Part I	±SD	Part II	±SD	Total	±SD
Sex (M = 1, F = 0)	0.13	0.35	0.15	0.37	0.14	0.36
Body surface area (m^2)	1.86	0.22	1.77	0.16	1.81	0.19
Age (years)	55.9	13.0	55.0	12.4	55.4	12.5
Prior cisplatin (yes = 1, no = 0)	0.26	0.46	0.25	0.44	0.26	0.44
Creatinine (mg/dl)	1.03	0.14	1.08	0.58	1.06	0.44
Creatinine clearance (ml/min)	69.1	19.9	83.5	36.3	78.9	32.3
Protein (mg/dl)	5.90	1.09	6.63	0.65	6.35	0.91
SGPT (units/l)	15.1	11.4	15.1	10.0	15.1	10.5
Alkaline phosphatase (units/l)	203	228	216	355	211	307
γ-GT (units/l)	49.4	90.0	44.4	69.5	46.7	78.3
Cisplatin dose (mg/m^2)	160	19.0	162	21.0	160	19.0
Etoposide dose (mg/m^2)	98.7	13.7	122	44.8	112	36.5
Infusion time (min)	73.2	27.4	76.4	37.6	75.0	33.2
Peak level (μg/ml)	24.2	14.5	23.4	6.21	23.7	10.4
AUC (μg min ml^{-1})	5,438	2,435	5,840	2,441	5,668	2,411
MRT (h)	5.78	1.96	7.25	1.81	6.62	1.98
$t_{1/2\alpha}$ (h)	0.31	0.11	0.57	0.22	0.47	0.23
$t_{1/2\beta}$ (h)	4.12	1.37	5.81	1.70	5.09	1.76
Vd_{ss} (l/m^2)	6.42	3.36	6.92	3.51	6.71	3.41
Cl (ml min^{-1} m^{-2})	21.3	7.63	18.0	6.28	19.42	6.99

Table 4. *P* values obtained in statistical analysis of clinical parameters versus pharmacokinetic parameters using Mann-Whitney's *U*-test

Clinical parameter	AUC	MRT	$t_{1/2a}$	$t_{1/2\beta}$	Vd_{ss}	Cl
Age of ≥60 years	$P \leq 0.01$				$P \leq 0.0001$	
Creatinine level of >1.2 mg/dl	$P \leq 0.0001$	$P \leq 0.0001$	$P \leq 0.0001$	$P \leq 0.0001$	$P \leq 0.0001$	$P \leq 0.0001$
Creatinine clearance of ≤70 ml/min	$P \leq 0.05$					$P \leq 0.05$
SGPT			$P \leq 0.0001$			
Protein					$P \leq 0.05$	$P \leq 0.01$

influence of clinical and laboratory data on the pharmacokinetic parameters was statistically significant. A value of $P \leq 0.05$ was assumed to indicate a positive correlation. When several kinetics were determined for one patient, only the mean values were entered in the statistical analysis of comparability and correlation (Tables 1–3).

Results

Comparison of pharmacokinetic data originating from the two parts of the study

In the present study, 62 measurements of kinetics in 35 patients were analysed. In general, etoposide infusions were given on 3 consecutive days. In Table 2, the pharmacokinetic data on all subjects are listed individually as the mean values for all kinetics measured in the same patient. Mean values for the clinical and pharmacokinetic parameters from both parts of the study are listed in Table 3 together with the values for the total study. Testing of linear regression between part I and part 2 revealed that the slope was nearly 1 and the correlation coefficient was 0.998. Thus, there was no statistically significant difference between the two parts. In the first part (including 15 patients), significant influences of patient-specific parameters on etoposide pharmacokinetics have previously been shown [20]. As the influence of clinical parameters such as impaired renal function and previous application of cisplatin became obvious, those patients were excluded from the final calculation of mean values; these exclusions reduced the difference between the mean values for the two parts of the study. Thus, the concerted statistical evaluation of both parts of the study, including all 35 patients and all 62 data for 24-h kinetics was possible.

Correlation between pharmacokinetic parameters and clinical conditions

The relatively high number of parameters modifying the pharmacokinetics of etoposide increase the probability that two or more parameters may interact in the same patient. By combining all data from the two parts of this study, we could examine this question in a larger number of patients. In all, 12 clinical parameters were recorded for each patient and were checked by Mann-Whitney's *U*-test of medians and then by multivariate analysis of medians for their potential influence on etoposide pharmacokinetics (Table 4). Of these 12 clinical parameters, 3 [age, reduced renal function (creatinine clearance, ≤70 ml/min) and previous application of cisplatin] exhibited significant influence on one or more pharmacokinetic parameters; non-significant correlations ($P > 0.05$) are not listed in Table 4.

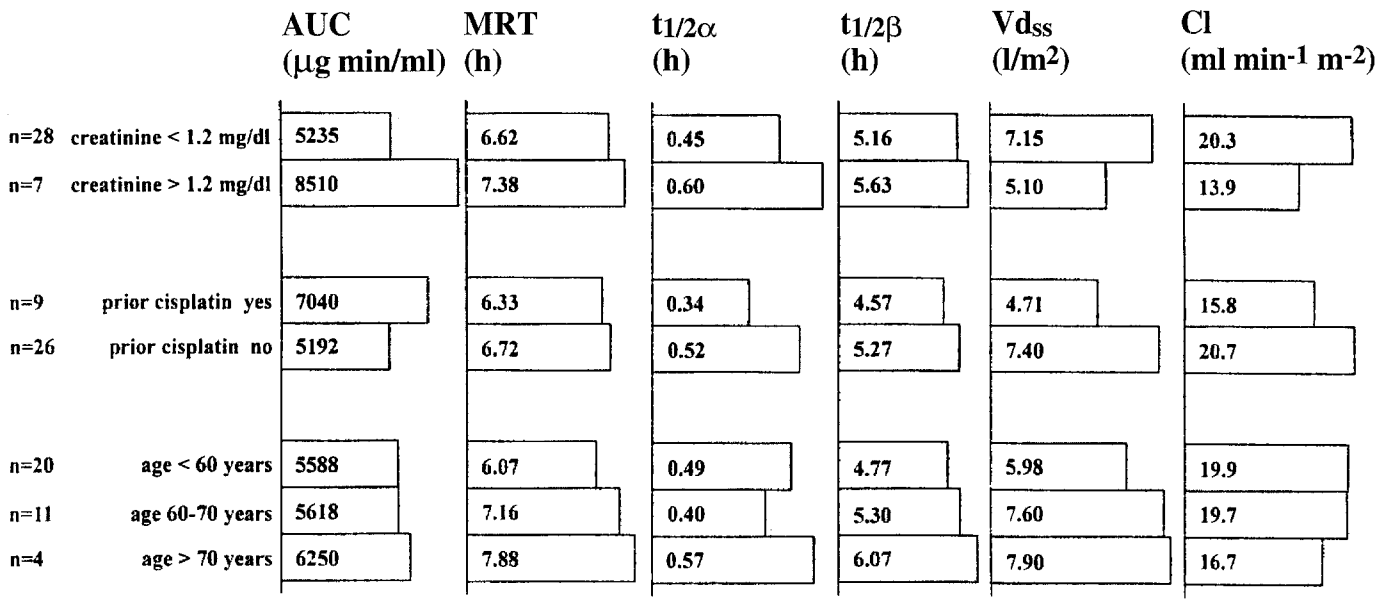

Fig. 1. Quantitative influence of renal impairment, prior application of cisplatin and increasing age on pharmacokinetic parameters (*columns 1–6*). *n*, Number of patients

Table 5. Summarised influence of three clinical conditions on pharmacokinetic parameters

	AUC	MRT	$t_{1/2\alpha}$	$t_{1/2\beta}$	Vd_{ss}	Cl
Renal impairment	↑	↑	↑	↑	↓	↓
Prior cisplatin	↑	↓	↓	↓	↓	↓
Increasing age	↑	↑	–	↑	↑	(↓)

The influence of the three clinical parameters renal impairment, prior application of cisplatin and increasing age on pharmacokinetic parameters is summarised in Table 5 in terms of tendency and in Fig. 1 in actual values; the significance of the correlation is shown in Table 4. The other nine clinical factors had no significant influence on pharmacokinetic parameters. The compartment-dependent parameter AUC was significantly elevated in patients who had previously received cisplatin, in those with reduced renal function, and in older patients (Table 5). The elimination half-life value $t_{1/2\beta}$ appeared to be higher in patients with renal impairment and in those who had undergone prior cisplatin treatment (Fig. 1, column 4). Interestingly, the $t_{1/2\alpha}$ value was altered in patients with renal impairment and in those showing higher levels of SGPT and γ-GT. We had no further clinical parameter to rate the liver function, but both elimination half-lives tended to be longer in patients with impaired liver function; for example, in one patient (K. M.) who showed extremely high values for the liver enzymes γ-GT, alkaline phosphatase and SGPT, all pharmacokinetic parameters differed widely from the overall mean values given in the Summary. As shown in Fig. 1 (column 6), both reduced renal function and prior cisplatin application independently lowered the systemic clearance (Cl) of etoposide, whereas age had a minor influence on this parameter. The volume of distribution at steady state (Vd_{ss}) was reduced in patients who had previously received cisplatin and in those with impaired renal function, whereas it was elevated in older patients (Fig. 1, column 5).

Assessment of the toxicity encountered in the present study was difficult because of the different polychemotherapy regimens used and the lack of knowledge of nadir blood values; blood cells were counted at the time at which the next chemotherapy cycle was scheduled. However, the pharmacokinetic results revealed a tendency for toxicity to be higher in patients who were older than 60 years, in those who had reduced renal and/or liver function and in those who had received etoposide chemotherapy in combination with cisplatin.

After the exclusion of patients who had previously been given cisplatin or who exhibited renal impairment and of one patient who showed extremely high levels of alkaline phosphatase, γ-GT and SGPT, the mean values calculated for the pharmacokinetic parameters evaluated were: $t_{1/2\beta}$, 4.9 ±1.2 h; MRT, 6.7 ± 1.4 h; AUC (AUC levels were normalized to a dose of 100 mg/m^2), 5.43 ± 1.74 mg min ml^{-1}; Vd_{ss}, 6.8 ±2.7 l/m^2; and Cl, 18.8 ± 5.3 ml min^{-1} m^{-2}.

Discussion

The statistical analysis between the clinical parameters and the pharmacokinetics of etoposide revealed that three factors, namely, renal function, previous application of cisplatin and age, cause significant alterations in etoposide pharmacokinetics. The correlations found in the present study are considered to be very valid for several reasons: (1) the high specifity and reproducibility of the assay used, (2) the large number of patients and of 24-h kinetic data and (3) the confirmation of the correlations previously found in the first part of the study.

All three clinical parameters mentioned above had significant influence on two or three different pharmacokinetic parameters as summarised in Table 5. The main elimination pathway for etoposide is via the kidneys; thus, impaired renal function results in a higher elimination half-life $t_{1/2\beta}$ value, an increased AUC, a lowered Vd_{ss} and reduced systemic clearance. These findings compare favourably with the results of other studies, although those studies included relatively small numbers of patients [2, 9]. In older patients, Vd_{ss} and AUC were elevated and the $t_{1/2\beta}$ value was higher than in younger individuals, whereas Cl was minimally altered. This constellation suggests deposition of the drug in deeper compartments. Thus far, this correlation has not been described in adults. In the first 15 patients evaluated [20], no concomitant drug except cisplatin showed a significant interaction with the disposition of etoposide. This finding was confirmed by the present study. Previous application of cisplatin reduced Vd_{ss}, $t_{1/2\alpha}$ and $t_{1/2\beta}$ values and Cl and increased the AUC value. This relationship suggests that the interaction of cisplatin with etoposide involves the inhibition of etoposide distribution rather than etoposide excretion.

Recently, Newell et al. [18] interpreted the interaction between etoposide and cisplatin as a possible acute deterioration of renal function following cisplatin infusion. However, this mechanism seems unlikely, as impaired renal function caused a completely different pattern of pharmacokinetic abnormalities in the present study (Table 5). Gouyette and co-workers [13] also addressed the question of possible interactions between cisplatin and etoposide. In 12 patients the authors did not find any drug interaction with cisplatin. However, they did not calculate the AUC and did not discuss the large variability observed in the volume of distribution (range, 2.07–9.95 l/m^2) and in plasma clearance (range, 20.7–44.8 ml/min). On the other hand, there is some in vitro and clinical evidence of synergy between cisplatin and etoposide. Recently, Tsai et al. [25] clearly demonstrated in eight lung-carcinoma cell lines that the synergy observed between cisplatin and etoposide was not due to a supra-additive effect at the cellular level. This finding is consistent with the interpretation of our results, as the pharmacodynamic synergy of these two drugs may be caused pharmacokinetically via alterations in etoposide distribution.

In conclusion the present study clearly demonstrates the high reproducibility and excellent practicability of the TLC/PDMS assay and elucidates the importance of an analytical method specifically designed for pharmacokinetics studies. Due to the numbers of patients (35) and of single 24-h kinetic data evaluated (62), for the first time a statistical comparison of patients with pharmacokinetically relevant, abnormal clinical factors became possible. Taking these factors into account, we regard the observed correlation between clinical parameters and etoposide pharmacokinetics to be very valuable. We found that renal dysfunction, advanced age and previous application of cisplatin had a highly significant influence on etoposide disposition. For several other parameters such as serum enzymes (SGPT, γ-GT) and serum proteins, marked but statistically insignificant influences were found. We suggest that in older patients and/or those with renal impairment constituting a higher risk for polychemotherapy, the dose of etoposide should be individually reduced. To enable the establishment of precise guidelines for modifications of the etoposide dose and to improve our understanding of the pharmacodynamic synergistic effects of this drug, we recommend that additional patients be carefully evaluated, whereby special attention should be focused on the side effects and on the therapeutic results obtained using polychemotherapy protocols.

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