Eur J Cancer Clin Oncol, Vol. 22, No. 10, pp. 1149–1155, 1986.
Printed in Great Britain

0277-5379/86$3.00+0.00
Pergamon Journals Ltd.

Pharmacokinetics of High Dose Etoposide (VP 16–213)*

JOOST J.M. HOLTHUIS,†¶ PIETER E. POSTMUS,§ WILLEM J. VAN OORT,‡ BRAM HULSHOFF,✱ HARRIËT VERLEUN,† DIRK TH. SLEIJFER‖ and NANNO H. MULDER‖

†*Department of Analytical Pharmacy, Subfaculty of Pharmacy, State University of Utrecht, Catharijnesingel* 60, 3511 *GH Utrecht*, ‡*Licentec, Churchilllaan* 11, 3527 *GV Utrecht*, §*Department of Pulmonary Medicine, and* ‖*Department of Medical Oncology, University Hospital Groningen, Oostersingel* 59, 9713 *EZ Groningen, The Netherlands*

Abstract—*This paper describes the pharmacokinetics of etoposide in cancer patients after high dose administration (up to* 3.5 g/m^2*). High performance liquid chromatography with electrochemical detection was used to determine etoposide,* cis *etoposide and the glucuronide of etoposide in plasma, bile, cerebro-spinal fluid, urine, saliva and ascites, the detection limit being* 2 ng *etoposide/*ml *plasma. The plasma concentration time curve shows a tri-phasic decay. The terminal phase is very slow. It was concluded that etoposide is strongly bound in the peripheral compartment. The volume of the central compartment varied from* 7.4 *to* 20.1 l *and the steady state volume of distribution from* 3.1 *to* 7.8 l/m^2*. Relatively high concentrations of etoposide were found in saliva, bile, ascites and urine and low concentrations in cerebro-spinal fluid. The total body clearance varied from* 12.0 *to* 26.8 ml/min/m^2*, and* 26.2 *to* 53.4% *was excreted as unchanged etoposide into the urine and* 8.3 *to* 17.3% *as glucuronide into the urine. Very low amounts of the* trans *hydroxy acid of etoposide and the* cis *etoposide were detected in the urine. Glucuronides were found in urine and duodenal fluid but not in plasma.*

INTRODUCTION

ETOPOSIDE is a semi-synthetic epipodophyllotoxin derivative, active against a variety of solid tumors [1, 2]. The standard dose, 200–400 mg/m^2 was defined in phase I studies [2, 3]. At this dose level pharmacokinetic studies defined an open two-compartment model [4–8]. The limited toxicity, primary myelosuppression, of etoposide at the standard dose level makes it a suitable drug for much higher dosages. Dosages up to 2.5 g/m^2 are considered to be possible without serious extramedullary toxicity [9, 10]. The pharmacological behaviour of the drug and its metabolites at this dose level are interesting, because if other myelotoxic drug are combined with high dose etoposide, the use of autologous bone marrow transplantation may become necessary [11]. The moment of bone marrow re-infusion depends in this situation on the level of drugs still present in the body.

In the only up till now reported study of the pharmacokinetics of high dose etoposide, the distribution and excretion were apparently not influenced by the dose [12]. In that study, however, data beyond 24 hr after the infusion were lacking and possible metabolites were not reported. In this report we describe the results of a more extensive pharmacological study of single agent high dose etoposide.

Accepted 17 February 1986.
*Supported in part by the Bristol Myers International Corporation
¶To whom requests for reprints should be addressed.
✱ Deceased 31 May 1986.

MATERIALS AND METHODS

Patients and therapy

Fourteen patients, 13 males, one female, with persistent or progressive malignant disease were treated with high dose etoposide [10]. Criteria for eligibility for the study were: Karnofsky score > 50, normal renal and liver function, informed consent (Table 1). This group of patients had besides normal bilirubin the following mean ± S.D. (range) renal and liver function parameters; serum creatinine 81 ± 20 μmol/l (50–113) and a serum glutamic oxaloacetic transaminase (SGOT) of 20 ± 5 U/l (10–32). All patients received etoposide on 3 consecutive days by six infusions at 12 hr intervals. Etoposide was dissolved in normal saline, maximum concentration, 0.8 mg/ml, and administered i.v. in 1–2 hr. Single doses over 800 mg were given in 2 hr. Except phenytoine (patient 12) no other medi-

Table 1. Patient characteristics

Patient number	Sex	Age (yr)	Body wt (kg)	Surface (m^2)	Total dose (g/m^2)	Diagnosis
1	M	53	72	1.8	0.5	Transitional cell cancer
2	M	47	55	1.7	0.5	Gastric cancer
3	M	56	65	1.9	1.0	Squamous cell lung cancer
4	M	55	98	2.4	1.5	Small cell lung cancer
5	M	53	60	1.7	1.5	Squamous cell lung cancer
6	M	56	88	2.2	2.0	Small cell lung cancer
7	M	48	83	2.2	2.5	Adenocarcinoma
8	M	40	86	2.1	2.5	Germ cell cancer
9	M	41	76	1.8	2.5	Germ cell cancer
10	M	21	92	2.2	2.5	Germ cell cancer
11	M	50	95	2.2	3.0	Small cell lung cancer
12	M	48	82	2.1	3.5	Germ cell cancer
13*	M	21	88	2.0	3.5	Germ cell cancer
14*	F	71	62	1.8	1.0	Cancer of the ovary

*These patients were not included in the pharmacokinetic study.

cation was co-adminstered which could be suspected from influencing the distribution and elimination from etoposide.

Drugs

Etoposide (Vepesid^R) and teniposide (Vumon^R) were obtained from Bristol Myers Nederland B.V. All other chemicals were of analytical grade and obtained from commerical sources and were used without further purification.

Sampling

Blood plasma was collected by an in-dwelling heparine lock which was placed in an arm vein opposite to the infusion site. Samples of 5 ml were collected in heparinized tubes and plasma was removed after centrifugation for 10 min at 4°C. The intention was to take blood plasma samples at 0, 1, 1.25, 1.5, 2, 3, 6, and 12 hr after each administration and also at 24, 36, 60, 84, 108, 132, 156 and 180 hr after the last administration. There were a few slight deviations from this sampling scheme. The exact sampling times were used for pharmacokinetic evaluation.

The urine excreted with 3–6 hr periods was collected and after homogenizing and cstablishing of the volume, a 100 ml sample was stored. The urine was collected for 168 hr after the first administration of etoposide.

Saliva samples were collected from a few patients at the same time as the plasma samples. To collect saliva the patient was asked to chew on a tablet of Teflon and 2 ml of the produced mixed saliva was stored.

Duodenal fluid was aspirated from the proximal part of the duodenum via a polyvinyl chloride tube already inserted for nutritional purposes. The position of the tube was controlled by X-ray fluoroscopy (patient number 13). Cerebro-spinal fluid (CSF) samples of 1.5 ml were taken from the Ommaya reservoir (patient number 12).

Ascites fluid samples of 1.5 ml were taken during percutane diagnostic or therapeutic puncture (patient number 14). All samples were frozen and stored at −20° C prior to analysis.

Analysis

Etoposide levels in biological fluids were measured by high performance liquid chromatography (HPLC) combined with electrochemical detection, as previously reported [13] using teniposide, a structure analog of etoposide as internal standard. At concentrations lower than 250 ng/ml, 1.0 ml of biological fluid was extracted with 2 ml 1,2-dichloroethane (DCE), at higher concentrations 0.1 ml of the biological fluid was sufficient for extraction with 1.0 ml DCE. The calibration samples were prepared by addition of etoposide to drug free biological fluids. These samples were analyzed simultaneously. Repeated determination of etoposide spiked plasma samples (concentration 50 resp. 500 ng/ml) showed a recovery of 97.8 ($n = 5$) resp. 98.5% ($n = 8$) with a relative S.D. of 3.6 resp. 3.1%. Recovery and relative S.D. of repetitive analysis of a spiked urine sample (507 ng/ml) proved to be 99.0% resp. 3.4% ($n = 6$).

Etoposide glucuronide was determined by analysis of etoposide after the enzymatic hydrolsis of the etoposide glucuronide. After addition of 100 µl of 0.1 M phosphate buffer pH 7 to 1.0 ml urine, the urine was extracted twice with 6 ml of DCE to remove the unchanged etoposide.

Subsequently 100 μl of the pre-extracted (etoposide-free) urine was transferred into a polypropylene tube. After addition of 1.0 ml 0.2 mM acetate buffer (pH 5.0) containing 2000 units β-glucuronidase (β-glucuronidase from bovine liver, Sigma Chemical Co.) per ml the mixture was incubated at 37° C during 16 hr. Etoposide which was liberated during the incubation was determined as described above. No etoposide was liberated when the pre-extracted urine was incubated in the absence of β-glucuronidase or in the presence of β-glucuronidase and 1,4-saccharolactone (an inhibitor of β-glucuronidase).

For the determination of the trans hydroxy acid of etoposide in urine, 25 μl of the pre-extracted (etoposide-free) urine (see above) is injected onto the HPLC system. Electrochemical detection at + 750 mV was used. The mobile phase consisted of a mixture of water, methanol and acetic acid (73 : 25 : 2 w/w). A μBondapack phenyl column and a flow of 1.0 ml/min was used. In the used chromatographic system the transhydroxy acid of etoposide showed a retention time of 8.0 min. The relative standard deviation for repeated injection of 25 μl of pre-extracted patients' urine containing 2.3 μg/ml of the transhydroxy acid derivative of etoposide is 4.3% ($n = 6$) [14]. The analytical methods used for the determination of etoposide and the metabolites are extensively described in refs. [13] and [14] resp.

Pharmacokinetic data analysis

Etoposide concentration–time curves are presented on a semi-logarithmic scale. The pharmacokinetic data analysis was performed with a NON–LIN computer program [15] extended by means of a Dirac Delta function to fit multiple dose data [16]. It was assumed that the disposition of etoposide did not vary from administration to administration. The log plasma concentration–time curves were fitted to an open three compartment model with elimination from the central compartment. From the fitting procedure the following parameters were obtained: V_c, the volume of the central compartment; k_e apparent first order elimination rate constant from the central compartment; the apparent first order intercompartmental transfer rate constants, k_{12}, k_{21}, k_{13}, and k_{31}. The rate constants α, β and γ and other pharmacokinetic parameters were calculated from the first order intercompartmental transfer rate constants as described by Gibaldi and Perrier [17]. The area under the plasma concentration-time curve (AUC) was calculated by numerical integration using trapezoïdal rule, from zero to the last measured concentration (< 0.2% of the peak concentration). The area under the moment curve (AUMC) (AUMC = ($c \times t$) vs. t) was calculated using the linear trapezoïdal method. Total body clearance (Cl_{tot} in ml/min/m^2) for the multiple i.v. infusions was calculated by dividing the total dose (D in mg) by the total AUC (mg.hr/l) and by the body area (m^2) of the patient. The renal clearance (Cl_{ren}) was calculated by dividing the total excreted amount of unchanged etoposide (in mg) in the urine by the plasma AUC. The clearance due to the renal excretion of etoposide glucuronide (Cl_{gluc}) was calculated by dividing the total amount of etoposide excreted as glucuronide by the AUC. The model independent steady state volume of distribution (Vd_{ss}) and the mean residence time (MRT in hr) of etoposide were calculated for multiple infusions, as described by Perrier and Mayersohn [18]. MRT was corrected for the infusion time.

RESULTS

Plasma concentrations of etoposide and metabolites

In 12 patients it was possible to measure plasma levels during and after the six infusions. The peak levels after the six infusions were not different, suggesting that cumulation did not occur.

After the first five infusions a bi-phasic decay was seen, however, after the sixth infusion a tri-phasic decay was found. The third phase was detectable approx. 25 hr after the administration. The plasma concentrations after 168 hr from the start of the infusions varied between 10 and 250 ng/ml (median 55, mean 66 ng/ml). A representative curve is shown in Fig. 1. Table 2 shows the parameters obtained from the curve fitting procedure, and the calculated pharmacokinetic parameters.

A linear relation (Fig. 2) was found between the total administered dose and the total AUC up to a dose of 3 g/m^2. The level of *cis* etoposide in the plasma is less than 5% of the etoposide plasma concentration. Other metabolities, i.e. the glucuronide of etoposide and the *trans* hydroxy acid of etoposide were not found in the plasma.

Renal exretion of etoposide and its metabolites

The total body clearance (Cl_{tot}), the clearance due to the renal excretion of unchanged etoposide (Cl_{ren}) and the clearance due to the renal excretion (Cl_{gluc}) are shown in Table 2. The amount of unchanged etoposide in the urine varied between 26.2 and 53.4% of the total administered dose, whereas the amount of the glucuronide of etoposide in the urine was 8.3–17.3% of the total dose. Together 34.5–66% of the amount administered etoposide is excreted into the urine.

The amount of the *trans* hydroxy acid of etoposide in the urine is very small (Table 3). The amount of the *cis* isomer of etoposide in the urine is < 1% of the administered dose.

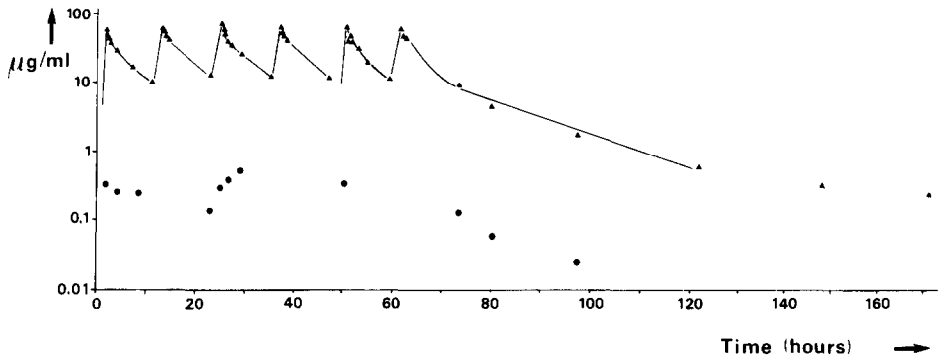

Fig. 1. Log plasma (▲) concentration and log CSF (●) concentration–time curve after administration of 6 × 1200 mg *etoposide (Patient 12).*

Table 2. Pharmacokinetic parameters

Patient	$t_{\frac{1}{2}}^{\alpha}$ (hr)	$t_{\frac{1}{2}}^{\beta}$ (hr)	γ (hr^{-1})	k_e (hr^{-1})	V_c (l)	Vd_{ss} (l/m^2)	Cl_{tot}	Cl_{ren} (ml/min/m²)	Cl_{gluc}	MRT (hr)	Dose (g/m^2)
1	0.42	3.80	$3.040\ 10^{-4}$	0.1798	7.4	3.1	26.8	14.3	3.4	3.14	0.5
2	1.55	9.72	$0.586\ 10^{-4}$	0.1283	10.9	4.5	16.2	6.0	2.8	4.63	0.5
3	4.06	45.59	$1.580\ 10^{-4}$	0.0675	13.2	4.2	16.8	4.4	1.4	4.17	1.0
4	2.23	14.17	$0.297\ 10^{-4}$	0.1573	12.6	4.2	20.6	5.6	2.4	3.14	1.5
5	3.53	14.90	$0.005\ 10^{-5}$	0.1010	11.9	5.1	18.8	7.1	2.3	4.28	1.5
6	3.18	19.09	$0.066\ 10^{-4}$	0.0981	12.7	4.8	12.0	n.d.	n.d.	5.36	2.0
7	3.51	10.39	$0.137\ 10^{-4}$	0.0660	12.6	4.1	14.1	5.9	2.0	4.84	2.5
8	1.82	16.15	$0.009\ 10^{-5}$	0.1877	9.6	4.4	17.4	8.9	2.5	4.32	2.5
9	3.78	14.59	$0.009\ 10^{-5}$	0.0896	13.8	5.3	15.5	n.d.	n.d.	4.75	2.5
10	0.49	6.54	$2.370\ 10^{-4}$	0.0906	10.5	3.7	13.5	n.d.	n.d.	4.52	2.5
11	3.46	99.00	$0.005\ 10^{-4}$	0.1108	14.7	4.7	15.1	6.5	1.5	3.96	3.0
12	3.82	23.90	$0.359\ 10^{-4}$	0.1341	20.1	7.8	26.0	8.2	4.4	5.17	3.5
median	3.32	14.75	$0.101\ 10^{-4}$	0.1059	12.6	4.5	16.5	6.4	2.4	4.42	–
mean	2.65	23.18	$0.68\ 10^{-4}$	0.1176	12.5	4.7	17.7	7.4	2.5	4.36	–
S.D.	1.31	26.17	$1.06\ 10^{-4}$	0.0406	3.1	1.2	4.7	2.9	0.9	0.70	–

n.d. = not determined

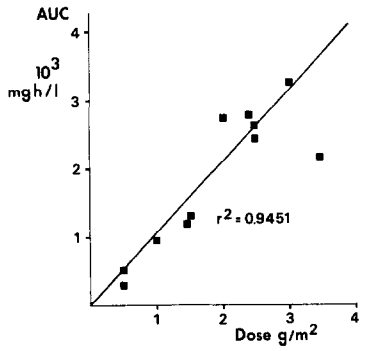

Fig. 2. Relation between the total area under the plasma concentration versus time curves (AUC) vs. the total administered dose.

In all patients the plateau of the cumulative excretion of etoposide and the metabolites was reached within 12 hr of the last infusion.

Distribution of etoposide into the saliva

The absolute amount of etoposide in the saliva is small; in Table 4 the saliva/plasma concentration ratios (*s/p*) are shown. These ratios were not different in the distribution phase and the elimination phase of the log plasma concentration times curves. The curves of the plasma concentration and saliva concentration vs. time run in parallel. The amount of etoposide bound to plasma albumin has been

Table 3. Excretion of etoposide (% of the total dose) as the trans *hydroxy acid of etoposide*

Patient	% of the total dose excreted
1	1.1
2	0.9
3	0.5
5	0.4
7	0.7
8	1.2
11	0.2
12	2.2
median	0.8
mean ± S.D.	0.9 ± 0.63
range	0.2 – 2.2

Table 4. Saliva concentration/plasma concentration ratios of etoposide in different patients

Patient	Mean saliva/plasma ratio × 100%	S.D.	Number of samples	Total dose (g/m^2)	Bound (%)
1	1.85	0.63	6	0.5	98.2
5	1.60	0.64	16	1.5	98.4
8	1.68	0.53	11	2.5	98.3
9	0.65	0.34	14	2.5	99.4
10	1.39	0.56	36	2.5	98.6
12	2.48	1.39	33	3.5	97.5
14	1.79	0.62	8	2.5	98.2

calculated by multiplicating (1-*s*/*p*) by 100% (see Table 4).

CSF concentrations of etoposide

In a patient the CSF levels were determined several times during the different infusions (Fig. 1). The amount of etoposide found in the CSF is low. The curves of Fig. 1 suggest that the penetration of etoposide into CSF is slower than the distribution into the central compartment, during the second phase the curves seem to run in parallel.

Etoposide concentrations in the bile

In one patient concentrations of etoposide and its metabolites were measured in the duodenal fluid during one infusion. The concentration of etoposide was 2–3 times higher than in plasma. The concentration of etoposide glucuronide was about 1/10 of the etoposide concentration. The peak of the etoposide glucuronide in the duodenal fluid appeared 45 min after the etoposide peak in the duodenal fluid. The curves are shown in Fig. 3.

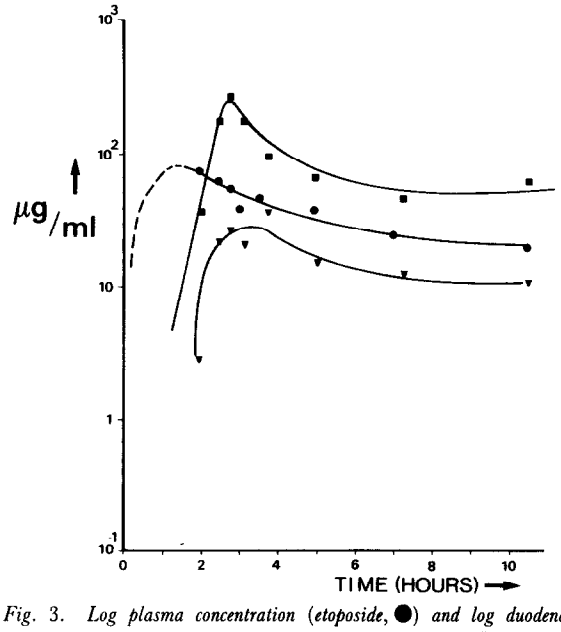

Fig. 3. Log plasma concentration (etoposide, ●) and log duodenal fluid concentration (etoposide ■ and etoposide glucuronide ▼) vs. time curve after administration of 1200 mg *etoposide in a* 2 *hr infusion (Patient* 13).

Penetration of etoposide into ascites

In one patient the etoposide concentrations were simultaneously determined in plasma and ascites. The distribution occurs at a lower rate than in plasma as can be seen in Fig. 4. Regarding the somewhat higher levels in the ascites during and after the fifth etoposide infusion compared with the first infusion there is a slower clearance from the ascites than from plasma, resulting in cumulation.

DISCUSSION

In this study a bi-phasic decay of the plasma concentrations was seen during the first five infusions. After the sixth infusion a tri-phasic decay was found; the time between two infusions was too short to find this third phase. The obtained plasma concentration curve were fitted to an open three-compartment model with the elimination from the central compartment, using a computer program which enables multiple dose data to be fitted. The data from this fitting process indicate that the half life time of the third phase is very long, the small number of data obtained during this period makes it not realistic to calculate this half-life time.

The found three-compartment model is in contrast with data from the literature. Pharmacokinetic studies [4–8, 12] of oral, standard dose i.v. or high dose i.v. etoposide all show an open two compartment model, however in all studies the sensitivity of the assay is too low or the studied period is too short to detect a third phase.

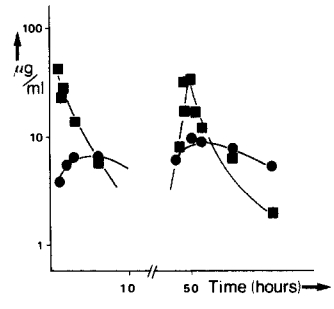

Fig. 4. Log plasma concentration (■) and log ascites (●) concentration time curve for etoposide after administration of 300 mg *etoposide in a* 1 *hr infusion (Patient* 14) *at* 0 *and* 48 *hr.*

The slow third phase indicates that part of the dose of etoposide is bound almost irreversibly to this tissue in the perpheral or deep peripheral compartment. This binding possibly partly explains the limited excretion of etoposide into the urine; only 44% of the i.v. dose of the labelled etoposide is excreted into the urine with 72 hr, measured as total radioactivity [4].

The linear relation, shown in Fig. 2, between the total administered dose and the total AUC, indicates the existence of linear pharmacokinetics up to a dose of 3.0 g/m^2 etoposide divided over six infusions in 3 days.

Cumulation, which might have been deduced from the increase in the peak concentration, was not observed during the six administrations. The total body clearance (Table 2), measured in this investigation, is significantly lower ($P = 0.01$) than the corresponding value presented by Hande *et al.* [12]: 17.7 ± 4.7 respectively 28.0 ± 9.7 ml/min/m^2. Hande *et al.* calculated the AUC value by extrapolating the plasma level of the last collected sample (at 24 hr after the last administration) to infinity. As a result of the extrapolation a slow terminal phase, if present, will result in an underestimate of the AUC, leading to a higher body clearance. This difference is of minor importance because the total body clearance in our study and in the study of Hande *et al.* [12] did not differ significantly from those found in studies after low dose etoposide [4–8].

The MRT found in this study is not significantly different from the MRT observed after low dose etoposide [19] (median 5.56 hr, range 2.52–9.95 hr). The apparent first order rate constants α and β are smaller than the values found in other studies [4–7, 12]. The half-life time of the β-phase is significantly higher when compared with the $t_{\frac{1}{2}}\beta$ found in other studies [4–8]. This is probably due to the mode of administration which might influence the distribution of etoposide. The amount of unchanges etoposide excreted into the urine indicates that this is a significant elimination pathway, although the interindividual variation is high. The amount of etoposide excreted after high dose makes it probably necessary to adjust the dose in the case of renal impairment whereas with low dose etoposide this is not necessary [20]. The distribution of etoposide into the saliva, a neutral compound at physiological pH, cannot be influenced by pH variations, it depends only on the lipophylicity and binding to plasma proteins. It was seen that the saliva and plasma concentration vs. time curve follow similar patterns: etoposide is excreted rapidly into the saliva. The salivary glands probably belong to the central compartment. Because the saliva/plasma concentration ratios show high inter-individual and intra-individual variations tha saliva should not be used to study the etoposide disposition. From the parallel plasma and saliva curves one can assume that the saliva concentration approaches the free etoposide concentration in the plasma, resulting in only a small variation of the fraction of etoposide bound to albumin in the plasma (mean 'bound' percentage of etoposide 98.4 ± 0.57%).

The found protein binding is higher than the protein binding found *in vitro* (94%) as determined by Allen [4].

Owing to the physico-chemical properties of etoposide, e.g. a lipophylic compound with some hydrophylic groups, its low solubility and its high mol. wt, it is likely that part of the dose will be eliminated by the liver and excreted into the bile. This is supported by the presence of etoposide in the faeces [5] of patients after parenteral administration. In rats etoposide and its glucuronide were found in the bile [21]. In one patient we detected higher levels of etoposide in the duodenal fluid than in the plasma, this proves that etoposide is actively excreted by the liver into the bile. The concentrations of etoposide in the duodenum are rather high assuming that the bile is diluted in the duodenum. The amount of the glucuronide of etoposide found in the duodenal fluid was ten times lower than the etoposide concentration and its excretion was delayed compared to etoposide.

The excretion of etoposide into the duodenum could be the start of an entero-hepatic cycle, however, the plasma concentration curve does not indicate the absorption of etoposide in the period between two infusions. This is in contrast with the known absorption of orally administered etoposide [22], although the absorbed amount can be ‹ 40% of the given dose. An important elimination pathway might be the metabolism of etoposide. Although the exact metabolic pattern is unknown, in this study glucuronidation proved to be the major metabolic pattern. The fact that no etoposide was liberated during the incubation of the urine with β-glucurondase/1,4-saccharolactone indicates that etoposide is not excreted as a sulphate conjugate.

The *trans* hydroxy acid of etoposide was found in small amounts in the urine. The importance of the metabolism for the elimination of etoposide was even more striking in patient 12 (Fig. 2). This patient received besides etoposide also diphantoine. In this patient the AUC showed a significant deviation from the linear relation between the total dose and the AUC (Fig. 2), and the amount of etoposide glucuronide and the *trans* hydroxy acid of etoposide (2.2% of the total administered dose) in the urine was high in comparison with the other patients. These effects of diphantoine on the total body clearance and non-renal metabolism of eto-

poside was also reported by Pfeffer et al. [19], and is probably based on the induction of enzymes responsible for the metabolism of etoposide.

The penetration of etoposide into the CSF is lower than was expected from the lipophylicity of etoposide, this is probably explained by the high protein binding of etoposide. Despite the low levels in the CSF the concentration of etoposide in brain metastases are apparently in the active range regarding the responses seen in patients with brain metastases of small cell lung cancer [23, 24].

REFERENCES

1. Issell BF. The podophyllotoxin derivatives VP 16–213 and VM 26. *Cancer Chemother Pharmcol* 1982, **7**, 73–80.
2. Arnold AM, Whitehouse JMA. Etoposide: a new anti-cancer agent. *Lancet* 1981, **ii**, 912–915.
3. Creaven PJ, Newman SJ, Selawry OS *et al.* Phase I clinical trial of weekly administration of 4′-demethylepipodophyllotoxin-9-(4,6-*O*-ethylidene-β-D-glucopyranoside) (NSC 141540; VP 16–213). *Cancer Chemother Rep* 1974, **58**, 901–907.
4. Allen LM, Creaven PJ. Comparison of the human pharmacokinetics of VM 26 and VP 16–213, two antineoplastic epipodophyllotoxin glucopyranoside derivatives. *Eur J Cancer* 1975, **11**, 697–707.
5. Creaven PJ, Allen LM. EPEG a new antineoplastic epipodophyllotoxin. *Clin Pharmacol Ther* 1975, **18**, 221–227.
6. Evans WE, Sinkule KA, Crom WA, Dow L, Look AT, Rivera G. Pharmacokinetics of teniposide and etoposide in children with cancer. *Cancer Chemother Pharmacol* 1982, **7**, 147–150.
7. D'Incalci M, Sessa C, Farina P *et al.* Clinical pharmacokinetics of VP 16. *Proc Am Assoc Cancer Res* 1982, **23**, 131.
8. D'Incalci M, Sessa C, Rossi C, Roviaro G, Mangioni C. Pharmacokinetics of etoposide in gestochoriocarcinoma. *Cancer Treat Rep* 1985, **69**, 69–72.
9. Wolff SN, Fer MF, McKay C *et al.* High dose VP 16–213 and autologous bone marrow transplantation for refractory malignancies, a phase I study. *J Clin Oncol* 1983, **1**, 701–705.
10. Postmus PE, Mulder NH, Sleijfer DT, Meinesz AF, Vriesendorp R, De Vries EGE. High dose etoposide for refractory malignancies, a phase I study. *Cancer Treat Rep* 1984, **68**, 1471–1474.
11. Postmus PE, De Vries EGE, De Vries-Hospers HG *et al.* Cyclophosphamide and VP 16–213 with autologous bone marrow transplantation, a dose escalation study. *Eur J Cancer Clin Oncol* 1984, **20**, 777–782.
12. Hande KR, Wedlund PJ, Noone RM, Wilkinson GR, Greco FA, Wolff SN. Pharmacokinetics of high dose etoposide (VP 16–213) administered to cancer patients. *Cancer Res* 1984, **44**, 379–382.
13. Holthuis JJM, Römkens FMGM, Pinedo HM, Van Oort WJ. Plasma assay for the antineoplastic agent VP 16–213 (etoposide) using high performance liquid chromatography with electrochemical detection. *J Pharm Biomed Anal* 1983, **1**, 89–97.
14. Holthuis JJM. Ph D Thesis, State University of Utrecht, The Netherlands, 1985.
15. Mezler CM, Elfring GL, McEwen AJ. A package of computer programs for pharmacokinetic modelling. *Biometrics* 1974, 562–563.
16. Howell JR. Non-linear regression on multiple-dose data. *J Pharmacol Biopharm* 1979, **7**, 675–678.
17. Gibaldi M, Perrier D. *Pharmacokinetics*, 2nd edn. New York, Marcel Dekker, 1982.
18. Perrier D, Mayersohn M. Non-compartmental determination of the steady state volume of distribution for any mode of administration. *J Pharm Sci* 1982, **71**, 372–373.
19. Pfeffer M, Nardella PA, Van Harken DR *et al.* The absolute oral bioavailability and pharmacokinetics of etoposide. In Issel BF, Muggia FM, Carter SK, eds.: *Etoposide (VP 16–213). Current Status and New Developments.* New York, Academic Press, 1984, 127–140.
20. Holthuis JJM, Van de Vijver FL, Van Oort WJ, Verleun H, Bekaert AB, De Broe M. Pharmacokinetic evaluation of increasing dosages of etoposide (VP 16–213) in a chronic hemodialysis patient. *Cancer Treat Rep* 1985, **69**, 1279–1282.
21. Colombo T, d'Incalci M, Donelli MG *et al.* Metabolic studies of a podophyllotoxin derivative (VP–16) in the isolated perfused liver. *Xenobiotica* 1985, **15**, 343–350.
22. Stewart DJ, Nundy D, Maroun JA, Treteault L, Prior J. Bioavailability, pharmacokinetics and clinical effects of an oral preparation of etoposide. *Cancer Treat Rep* 1985, **69**, 269–273.
23. Postmus PE, Holthuis JJM, Haaxma-Reiche H *et al.* Penetration of VP 16–213 into cerebrospinal fluid after high dose intravenous administration. *J Clin Oncol* 1984, **2**, 215–220.
24. Postmus PE, Haaxma-Reiche H, Vencken LM, Meinesz AF, Sleijfer DTh, Mulder NH. Remission of brain metastases from small cell lung cancer after high dose chemotherapy. *Ann Int Med* 1984, **101**, 717.