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Pharmacokinetics of teniposide (VM 26) after IV administration in serum and malignant ascites of patients with ovarian carcinoma

P. Canal, R. Bugat, C. Michel, H. Roche, G. Soula, and P. F. Combes †

Groupe de Recherches Carcinologiques, Centre Claudius-Regaud, 20–24 rue du Pont-Saint-Pierre, F-31052 Toulouse, France

Summary. *Nine patients with ovarian carcinoma and malignant ascites treated with IV teniposide chemotherapy (30 mg/m²/30 min) entered this study. Plasma and peritoneal fluid levels were measured by an HPLC method with electrochemical detection. Plasma decay kinetics followed a triexponential function. A high variability of drug diffusion in ascites was noticed. Peak concentrations in ascites ranged from 1.6% to 20.5% of serum peak concentration. The concentration in peritoneal fluid reached a maximum level 6 h after the infusion ended. Teniposide was less slowly eliminated from ascites than from serum. The exposure of the inflammatory peritoneal fluid to the drug expressed by area under the concentration-time curve (AUC) was also subject to significant interindividual variation, ranging from 223 to 2332 μg/ml × min. However, the peritoneal AUC was correlated with serum AUC and with the systemic clearance of the drug. A significant relationship between gamma glutamyltranspeptidase and both systemic clearance and either the serum or the peritoneal AUC was found, suggesting that liver plays a role in drug disposition.*

Introduction

In the last decade, the semisynthetic derivative of epipodophyllotoxin, teniposide (VM26), has gained in importance because of its effectiveness against a variety of experimental and human tumors [3, 4, 11, 14], especially ovarian carcinoma [12, 19]. This is the fourth leading cause of cancer death in women [17]. One of the poor prognosis factors is its propensity to develop intra-abdominal dissemination and malignant ascites constitutes a common clinical problem of this solid tumor. The data available on the disposition of teniposide in malignant peritoneal effusion after IV administration of the drug are limited [2, 16]. This study was undertaken to analyze the diffusion of VM26 in ascites of ovarian carcinoma and to compare the pharmacokinetics in plasma and ascites.

Materials and methods

Patients. Nine patients with serous ovarian epithelioma (mean age 65.1 years) with microscopically proved malignant ascites entered the study. Inclusion criteria were serum creatinine level less than 130 μmol/l, blood urea nitrogen less than 7 mmol/l, leukocyte and platelet counts greater than 3000/mm³ and 100 000/mm³, respectively, and a normal bilirubin serum level. All patients had previously received different chemotherapy regimens. No patient had received irradiation to the peritoneal cavity.

Drug treatment. Teniposide was administered IV infusion over 30 min (30 mg/m² in 125 ml 0.9% NaCl solution).

Sample collection. For each patient, blood and ascites samples were collected in dry tubes. Samples were taken before VM26 administration, at the end of the infusion, and at 5, 10, 15, and 30 min and 1, 2, 4, 6, 12, 24, 36, and 48 h after the infusion ended. The repeated peritoneal punctures were performed through a single path. Serum and ascites aliquots were frozen at −20 °C until analyzed.

Drug assay. The concentration of VM26 in serum and peritoneal samples was assayed in duplicate by a high-performance liquid chromatography method with electrochemical detection. A volume of 10 μl etoposide (VP16-213) was added as internal standard to 1 ml plasma or ascites. After extraction with 5 ml chloroform, the organic phase was dried under vacuum and then redissolved in 200 μl of the mobile phase. Then 20 μl of this solution was injected onto a Waters Model 6000 A high-performance liquid chromatograph. Separation was achieved with an isocratic solvent system of water (45%), methanol (54%), acetic acid (1%), and 250 mmol ammonium acetate at a flow rate of 1.5 ml/min using a 30-cm-long μ Bondapack C 18 (10 μm) column. The electrochemical detection apparatus used comprised a Faraday cage enclosing a TL-5 glassy carbon electrode and an LC-4 controller, both purchased from Bioanalytical Systems (West Lafayette, Ind, USA). The electrochemical potential was set at +900 mV against an Ag/Ag Cl reference electrode. The detection limit of VM26 in this system was 20 ng/ml. The assay's percentage coefficient of variation, on a day-to-day basis, was 6.3%.

Pharmacokinetic calculations. The following formulae were used for pharmacokinetic evaluation.

AUC = area under the plasma or ascites concentration-VS-time curve ($0 \rightarrow \infty$) extrapolated to infinity (trapezoidal method) expressed in micrograms per milliliter per minute

† Deceased

Offprint requests to: P. Canal

Vdss = apparent volume of distribution l/m^2 = $\frac{\text{Dose } \mu g/m^2}{AUC \times \gamma}$

γ = apparent first-order rate constant for elimination of drug from the body

Clp = systemic clearance = $\frac{\text{Dose } \mu g/m^2}{AUC\ (0 \rightarrow \infty)}$

Statistical analysis. Simple linear regression analysis was performed to identify significant ($P < 0.05$) relationships between various pharmacokinetics parameters (AUC, Clp, Vd_{ss}) and patient biochemical variables. When necessary, appropriate log transformations were carried out to normalize distributions and to stabilize variances.

Results

Following the infusion period VM26 disappeared from plasma following a triphasic pattern. Table 1 summarizes the blood pharmacokinetic parameters of the patients. The mean sequential concentrations of VM26 vs time are shown in Fig. 1. Initial VM26 plasma levels ranged from 2.7 to 9.3 μg/ml and declined with mean (±SD) half-lives of 56±23 min, 4.45±1.47 h, and 20.3±4.94 h.

The systemic clearance and the steady-state volume of distribution were, respectively, 16.80±5.35 ml/min/m^2 and 29.75±9.63 l/m^2.

A high variability in peritoneal levels was noted (Fig. 2), with peak values ranging from 110 ng/ml up to 1693 ng/ml. However, this maximum concentration was reached between 6 and 12 h after the infusion ended (Table 2). Serum and ascites levels were equal after 24 h for seven of our nine patients. In the two remaining cases, the ascites/serum ratio concentration remained below 0.25.

In seven cases, peritoneal levels declined more slowly than serum levels. As shown in Table 2, the half-life of the terminal elimination phase in ascites ranged from 36.1 to 65.0 h, while serum T½ varied between 17.1 and 27.4 h. For the two other patients, who had the highest drug diffu-

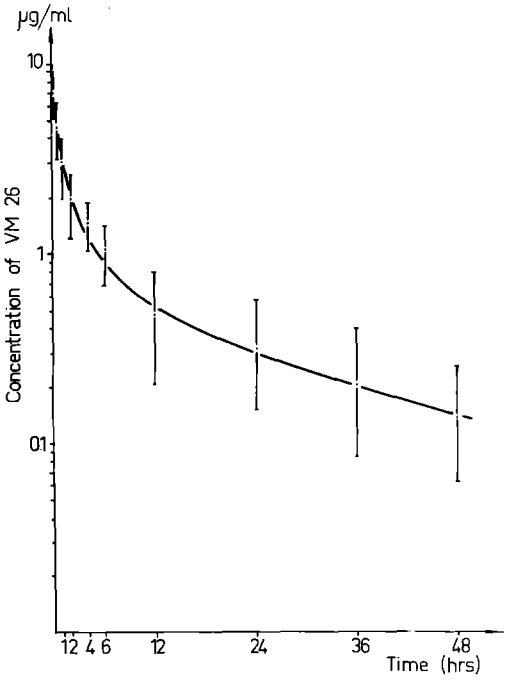

Fig. 1. Semilogarithmic plot of mean serum concentration (±SD) of VM26 vs time following IV administration of 30 mg/m^2 in nine patients suffering from ovarian carcinoma with malignant ascites

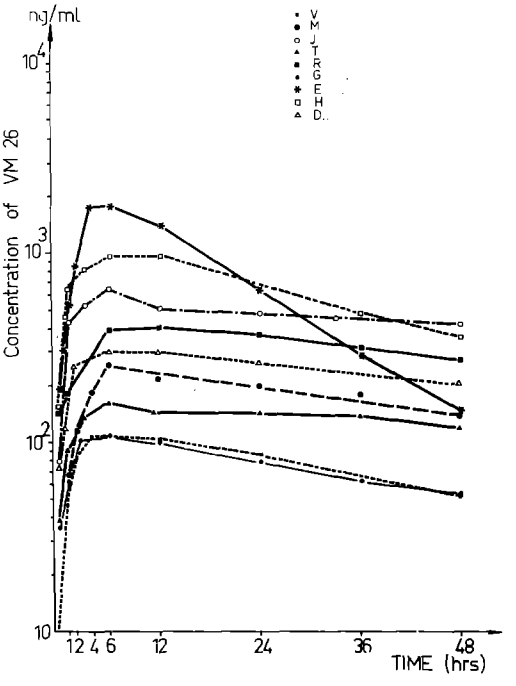

Fig. 2. Semilogarithmic plot of ascites concentration of VM26 vs time following IV administration in nine patients suffering from disseminated ovarian carcinoma

Table 1. Pharmacokinetic parameters of VM26 after IV administration to patients suffering from ovarian carcinoma

	A (μg/ml)	α (min^{-1})	T½ α (min)	B (μg/ml)	β (h^{-1})	T½ β (h)	C (μg/ml)	γ (h^{-1})	T½ γ (h)	AUC (μg/ml × min)	Clp (ml/min/m^2)	Vd (l/m^2)
G	6.501	0.0127	54	2.24	0.0964	7.18	0.7978	0.0288	24.1	1887	15.66	33.12
V	2.69	0.0072	96	1.33	0.904	3.72	0.96	0.0347	17.3	1489	20.14	34.83
T	8.536	0.0187	37	2.49	0.1802	3.84	0.317	0.0405	17.1	1950	15.38	22.78
M	6.38	0.0173	40	1.02	0.115	6.01	0.397	0.0385	18.1	1160	26.08	40.65
D	6.871	0.0169	41	2.29	0.211	3.28	0.511	0.0328	21.1	1258	23.85	43.60
J	7.840	0.0144	48	2.22	0.1211	5.72	0.8384	0.0253	27.4	2319	12.97	30.75
R	9.370	0.0079	87	4.45	0.1957	3.54	0.292	0.0306	22.6	2170	13.83	27.11
H	7.441	0.0095	72	4.18	0.182	3.80	0.471	0.0288	24	2883	10.41	21.68
E	7.961	0.0213	32	4.11	0.235	2.95	2.07	0.0587	11	2320	12.94	13.23

Table 2. Comparison of serum and ascites pharmacokinetic parameters of VM26 after IV administration in patients with disseminated ovarian carcinoma

Patient	Peritoneal fluid protein (g/l)	Peak concentration (ng/ml)		Half life of terminal elimination phase (h)		AUC ($0 \rightarrow \infty$) (μg/ml × min)		Clearance (ml/min/m^2)	
		Serum	Ascites	Serum	Ascites	Serum	Ascites	Peritoneal	Systemic
G	18	6800	110	24.1	36.5	1887	223	201	15.89
V	40	2820	113	17.3	36.1	1489	283	158.7	20.14
T	49	8100	164	17.1	60.2	1950	510	88.1	15.83
M	38	5940	255	18.1	53.7	1160	536	84.03	26.08
D	42	6935	313	21.1	65.4	1258	755	59.64	23.85
J	54	8200	678	27.4	60	2319	1432	31.41	12.97
R	31	9300	422	22.6	57.8	2170	1442	31.22	13.83
H	48	7400	1030	24	24	2883	2332	19.30	10.41
E	53	8260	1693	11	11	2320	2104	21.40	12.94

sion in the peritoneum, levels declined in parallel with those in serum. The high variability in drug diffusion across peritoneum is emphasized by pharmacokinetic evaluation of ascites AUC: levels differed by a factor of 10 and the ascites/serum AUC ratio, between 0.12 and 0.91.

Figure 3 summarizes a study of simple linear regression analysis between pharmacokinetic parameters and biochemical variables. Log (GGT) is correlated both with serum (Fig. 3a) and peritoneal AUC, and also with systemic clearance. A significant relationship is observed between serum pharmacokinetic parameters (AUC, Clp., Vd_{ss}) and peritoneal AUC (Fig. 3b). On the other hand, the volume of distribution at steady-state is correlated with log (albumin) ($r=0.749$, $P<0.02$) (Fig. 3c). A significant correlation is also found between logarithm of peritoneal fluid protein and both peritoneal clearance ($r=0.710$, $P<0.05$) (Fig. 3d), and the peritoneal clearance/systemic clearance ratio ($r=0.747$, $P<0.02$).

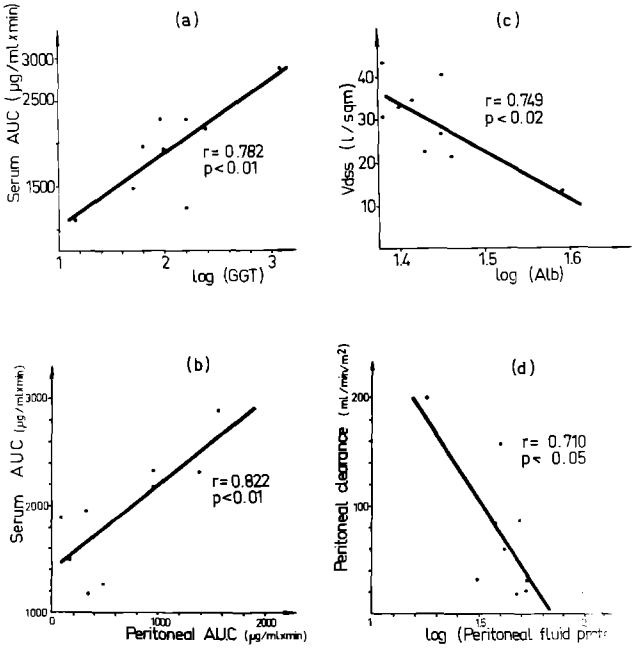

Fig. 3 a–c. Significant relationships identified by simple linear regression analysis of serum AUC. **(a, b)**, Vd_{ss} **(c)** and peritoneal clearance **(d)** in patients with disseminated ovarian carcinoma

Discussion

While teniposide is widely used in systemic chemotherapy of ovarian carcinoma, few authors have studied VM26 pharmacokinetics in cases of malignant ascites [2, 16].

In our report, as in the studies of Allen and Creaven [1] and Creaven [5], VM26 plasma decay kinetics follow a triexponential function, which differs from previous data recorded in adults [6] and children [4, 7], where biexponential decay is described.

As in many other reports [1, 18] a high interindividual variability in pharmacokinetic parameters is observed, which leads us to wonder whether the administration of a drug in doses related to body weight or body surface area really does ensure that each patient is effectively exposed to comparable amounts [8].

The strong correlation between elevated GGT and diminished systemic clearance or increased serum AUC underlines, as reported by Sinkule et al [18], the suspected role of the liver in drug distribution. From this point of view, previous pharmacokinetic studies [15] have shown VM26 to be conjugated by the liver as glucuronide or sulfate derivatives, and to be predominantly excreted via bile. A diminished systemic clearance may be related to hepatic cellular damage or hepatic obstruction by tumor, as reflected in elevated serum GGT.

In addition, we note a relationship between Vdss and serum albumin, which suggests that VM26 bioavailability is influenced by protein binding. In vitro analysis of protein binding to human serum albumin has emphasized that the physiological magnitude of the binding of VM26 is sufficient ($>10^4\ M^{-1}$) to influence the distribution and elimination of this drug in vivo [9].

Our study demonstrates that although the diffusion of teniposide across the peritoneal membrane can vary from patient to patient by a factor of 10, it is significantly related to serum pharmacokinetic parameters (AUC, Clp, Vd_{ss}).

The interindividual variabilities in peritoneal drug diffusion already underlined by Sessa et al. [16] can be explained to some extent by the fact that patients have varying volumes of ascites with different protein concentration. According to the molecular weight and lipid solubility of the drug, direct instillation of teniposide into the peritoneal cavity in patients with ovarian cancer (phase I trial) should let us know whether a higher drug concentration

could be achieved with acceptable local toxicity. The recently reported phase I trials of IP cisplatin [13] and melphalan [10] have already shown a pharmacologic advantage for IP administration. Epipodophyllotoxin derivatives given IP might be expected to have a lower dose-limiting toxicity from systemic drug effects.

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