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Clinical pharmacology of intracarotid etoposide*

Niramol Savaraj[1], Lynn G. Feun[1], Katherine Lu[1], Sidney Wallace[2], William S. Fields[1], and Ti Li Loo[1]

[1] Division of Medicine, [2] Division of Radiology The University of Texas Cancer Center M. D. Anderson Hospital and Tumor Institute Houston, TX 77030, USA

Summary. Pharmacokinetics studies were performed in ten patients who received VP-16 by intracarotid infusion at 100–300 mg/m^2. VP-16 was analyzed by high-pressure liquid chromatography. ESTRIP and NONLIN were used to characterize VP-16 pharmacokinetics. VP-16 disappeared biphasically, with a $t_{1/2}$ β of 6.1 ± 1.4 h; the total clearance was 26.8 ± 2.8 ml/min/m^2, and the V_{ss} was 8.8 ± 1.6 l/m^2. The pharmacokinetics was not significantly different after administration by the IV route. However, at a lower dosage, < 140 mg/m^2, the half-life appears to be shorter. This may or may not be significant, since VP-16 pharmacokinetics is quite variable and the number of patients studied is relatively small. Overall, the brain and brain tumor do not appear to have any first-pass effect on VP-16 pharmacokinetics.

Introduction

Etoposide (VP-16), a derivative of podophyllotoxin, has shown antitumor activity against small cell lung cancer, malignant lymphoma, and testicular cancer [2–5, 8, 18]. Little is known about its activity against primary central nervous system (CNS) neoplasms. The clinical pharmacology of VP-16 is well known [1, 6, 7, 9, 16]. Although the cerebrospinal fluid (CSF) penetration of VP-16 is relatively poor [6], with a higher dosage drug concentrations of 0.1–1.4 μg/ml were achieved in the CSF [13]. We studied the tissue penetration of VP-16 into the CNS and confirmed that the penetration of the drug is relatively unimpressive [11]. In contrast, its analogue VM-26 has been shown to have some activity against primary CNS neoplasms when administered IV [17]. In addition, intracarotid VM-26 has been reported to elicit impressive responses in ten patients with brain tumors [12]. We conducted a pharmacological and toxicity study of intracarotid VP-16 in dogs, and found that high drug concentrations could be achieved in tissue, with tolerable toxicity [14]. In conjunction with our ongoing phase I–II study of intracarotid VP-16 in patients with unresectable brain tumors, we have therefore studied the pharmacology of intracarotid VP-16.

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Offprint requests to: N. Savaraj, University of Miami, Papanicalion, Cancer Center 1475 NW 12th Ave. Miami, Fl 33136, USA

Materials and methods

The pharmacokinetics of VP-16 was determined in 11 courses administered to 10 patients, 9 of whom had primary malignant brain tumors and one, metastatic malignant melanoma. A percutaneous catheter was inserted transfemorally into the internal carotid artery on the involved side and VP-16 was then infused over 60–90 min. The dosage of VP-16 ranged from 100 to 300 mg/m^2. One patient (no. 6) was studied twice at different dosage levels. All patients had normal liver chemistries and normal serum BUN and creatinine values prior to treatment.

Blood samples were obtained at 0, 15, 30, 45, 60 min and 1, 2, 4, 6, 8, 24 h after completion of the infusion. Fractional urine collection was obtained for 24 h after VP-16 administration.

VP-16 was measured by the high-performance liquid chromatography (HPLC) method of Sealze et al. [15]. Briefly, 2 ml plasma or urine was extracted twice with 6 ml chloroform. The extract was evaporated to dryness under a stream of nitrogen, and the residual was reconstituted with 70% acetonitrile for injection into the HPLC. The elution

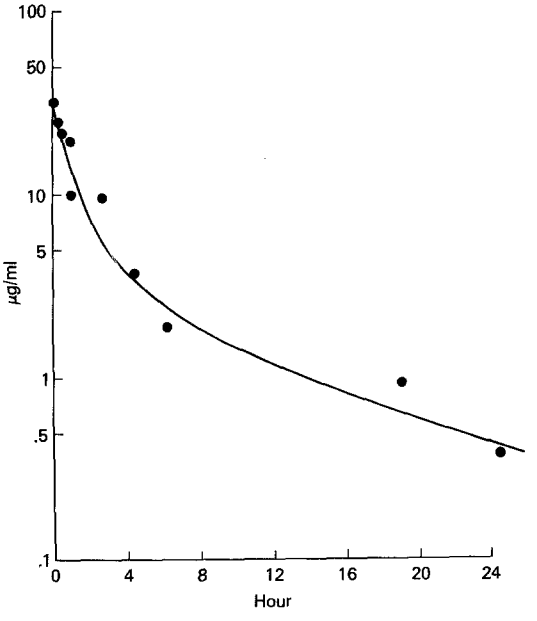

Fig. 1. Plasma disappearance of VP-16 in patient 6, who received 160 mg/m^2 by the intracarotid route

was accomplished with a Waters Bonapak CN column, which was eluted with 0.02 *M* acetate buffer (pH 4.0) in 85% acetonitrile at a flow rate of 1.5 ml/min. The UV monitor was set at 254 nm. The sensitivity of the assay was 0.1 μg/ml. The retention time of VP-16 was 12 ± 1 min.

Pharmacokinetic analysis. Nonlinear least-square regression analysis of the data was carried out on a CYBER 174 computer system using the ESTRIP and NONLIN program. All data points were appropriately weighted with reciprocal drug concentration. The goodness of fit was based on correlation coefficient, F-test and AKAIKI's criteria information. All pharmacokinetic parameters were corrected for infusion time using the method of Loo and Riegleman [10].

Results

The two-compartment open model seems to give the best fit of the postinfusion plasma VP-16 disappearance curve (Fig. 1). The pertinent pharmacokinetic parameters are listed in Table 1. In patient 6, who received two courses of VP-16 at different dosage levels, there were no significant differences in these parameters in the two courses. The 24-h cumulative urinary excretion were completed in four patients, and the mean cumulative urinary excretion was 17.8% ± 4.1% of the administered dose. Although the pharmacokinetic parameters vary considerably, they appear to fall into two groups with regard to the elimination half-lives (Table 2). These half-lives apparently become longer when the dose exceeds 140 mg/m^2 ($0.01 < P < 0.05$). Our results were not significantly (Table 3) ($P > 0.1$) different

Table 1. Pharmacokinetic parameters of VP-16 following IC administration

Patients	Dose (mg/m^2)	T ½		Cl (ml/min per m^2)	K_{12} (h^{-1})	K_{21} (h^{-1})	K_{el} (h^{-1})	V_{ss} l/m^2	V_c l/m^2	Va l/m^2
		α (min)	β (h)							
1	100	18.2	3.2	45.6	1.00	0.57	0.98	8.3	2.8	12.5
2	130	15.9	2.8	29.2	1.22	0.97	0.66	6.0	2.7	7.1
3	130	3.2	1.5	20.8	6.12	0.99	0.01	1.5	2.1	2.6
4	140	3.9	1.6	30.6	6.79	2.44	1.85	6.9	1.8	9.8
5	160	2.6	6.4	12.7	9.41	1.24	1.00	6.4	0.8	6.9
6	160	37.5	5.7	22.2	0.49	0.43	0.31	9.1	4.3	11.0
[a]	200	1.3	6.9	28.8	0.11	0.14	0.39	9.8	4.6	17.1
7	200	53.4	15.5	30.2	0.22	0.06	0.54	14.8	3.4	40.6
8	200	55.3	13.4	33.6	0.31	0.94	0.39	21.9	5.1	40.6
9	250	71.4	4.9	26.5	0.11	0.19	0.42	5.9	3.8	11.2
10	300	5.7	5.3	14.4	0.19	0.46	0.20	6.6	4.6	6.6
Mean ± SE		24.4 ± 7.7	6.1 ± 1.4	26.8 ± 2.8	2.36 ± 1.02	0.78 ± 0.20	0.61 ± 0.15	8.8 ± 1.6	3.3 ± 0.4	15.1 ± 3.9

[a] Same patient at different dosage

Table 2. Pharmacokinetic parameters of VP-16 by the intracarotid route at different dosages

Dose (mg/m^2)	T ½		Cl (ml/min per m^2)	K_{12} (h^{-1})	K_{21} (h^{-1})	K_{el} (h^{-1})	V_{ss} l/m^2	V_c l/m^2	Va l/m^2
	α (min)	β (h)							
100–140 $n = 4$	10.3 ± 3.9	2.3 ± 0.4	31.5 ± 5.2	3.78 ± 1.55	1.24 ± 0.41	0.88 ± 0.38	5.7 ± 1.5	2.4 ± 0.2	8.0 ± 2.1
160–200 $n = 7$	32.5 ± 10.9	8.3 ± 1.6	26.8 ± 2.8	1.55 ± 1.31	0.49 ± 0.17	0.46 ± 0.10	10.6 ± 2.2	3.8 ± 0.5	19.1 ± 5.7
t-test	NS	$0.02 < P < 0.05$	NS	NS	NS	NS	NS	NS	NS

NS, not significant

Table 3. Comparison of pharmacokinetics parameters following intracarotid vs intravenous administration

Dose (mg/m^2)	T ½			Cl (ml/min per m^2)	K_{12} (h^{-1})	K_{21} (h^{-1})	K_{el} (h^{-1})	V_{ss} l/m^2	V_c l/m^2	Va l/m^2
	Route	α (min)	β (h)							
100–300 $n = 11$	IC	24.4 ± 7.7	6.1 ± 1.4	26.8 ± 2.8	2.36 ± 1.02	0.78 ± 0.20	0.61 ± 0.15	8.8 ± 1.6	3.3 ± 0.4	15.1 ± 3.9
100–200[a] $n = 14$	IV		7.1 ± 0.7	26.8 ± 2.4						15.7 ± 1.8
200–290[b] $n = 11$	IV		8.2 + 1.1	27.07	0.56 ± 0.68	0.40 ± 0.39	0.32 ± 0.09	10.6	4.4	+ 16.0

[a] [7]

[b] [1] The clearance and volume of distribution values were converted from liters per kilogram

from those of D'Incalci et al [7] and Allen et al [1], who administered VP-16 by the IV route. However, with the intracarotid (IC) route and lower doses the elimination half-lives of the drug were shorter ($P < 0.01$).

Discussion

When administered by way of the internal carotid artery, VP-16 may be subject to the possible first-pass effects of the brain tissue, including binding and metabolism, in a manner analogous to the hepatic first-pass effects exerted on an orally administered drug. We previously demonstrated the presence of the hydroxy-acid metabolite of VP-16 in the brains of dogs that received the drug by the intracarotid route [14]. The same metabolite was also identified in the CSF of patients who received VP-16 [13], although it was not clear whether the metabolite was actually formed in the brain. The present investigation was undertaken to determine the first-pass effects of the brain on VP-16 pharmacokinetics when the drug was administered intra-arterially.

Our results were not significantly different from those reported by others who administered the drug IV. Therefore, if the brain conferred any first-pass effects on VP-16 pharmacokinetics, they were too small to be determined. However, in our studies, with the dose below 140 mg/m^2 the elimination half-life of VP-16 was much shorter than at higher doses, 2.3 h versus 8.3 h, and the apparent of volume of distribution computed from the area under the plasma VP-16 concentration versus time curve was smaller, 8 l/m^2 as compared with 19.1 l/m^2, because the pharmacokinetics of VP-16 is quite variable. The short half-life seen at lower dosages might prove not to exist if more patients were studied. However, if this is a true phenomenon, it seems that increasing the dose may cause an increasing amount of VP-16 to become localized in the brain by binding the receptors, which may become saturable at higher doses. Since myelosuppression was not a significant problem in our clinical trial, and the solubility of VP-16 may preclude the use of high doses of the drug by the IC route, it seems logical to administer VP-16 more frequently but at small doses. Further clinical testing will be needed to explore this possibility.

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