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Penetration of etoposide into human malignant brain tumors after intravenous and oral administration

Katsuzo Kiya, Tohru Uozumi, Hidenori Ogasawara, Kazuhiko Sugiyama, Takuhiro Hotta, Takashi Mikami, and Kaoru Kurisu

Department of Neurosurgery, Hiroshima University School of Medicine, Hiroshima, Japan

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Summary. Penetration of etoposide into the cerebrospinal fluid, brain tumor, and brain tissue after intravenous administration was investigated in patients presenting with malignant brain tumors. A relatively low dose (55–65 mg/m^2) was used to compare intravenous with oral administration. High-performance liquid chromatography with fluorescence detection was used to evaluate drug levels. Plasma and cerebrospinal fluid levels of etoposide after oral administration (50–150 mg/day) were also studied so as to determine the adequate oral dose for the treatment of malignant brain tumors. The peak plasma concentration after intravenous administration ranged from 7.01 to 10.47 μg/ml, varying in proportion to the injected dose, whereas that after oral administration was lower, namely, 1.44–4.99 μg/ml, and was unstable when the oral dose was 150 mg daily. The peak cerebrospinal fluid level following either intravenous or oral administration was much lower than the plasma concentration and was influenced by the peak plasma level and the sampling site. The etoposide concentration in cerebrospinal fluid taken from the subarachnoid space and ventricle of patients displaying no tumor invasion and of those presenting with meningeal carcinomatosis and in cerebrospinal fluid taken from the dead space after tumor resection was 0.7% ± 0.5%, 3.4% ± 1.0%, and 7.2% ± 8.5%, respectively, of the plasma concentration. Serial oral administration did not result in the accumulation of etoposide in cerebrospinal fluid. The tumor concentration (1.04–4.80 μg/g) was 14.0% ± 2.9% of the plasma level after intravenous administration, was related to the injected dose, and was approximately twice the concentration detected in the brain tissue. Therefore, a relatively low dose of etoposide injected intravenously penetrates the brain tumor at an efficacious concentration. Our results indicate than an oral dose of 100 mg etoposide be given for malignant brain tumors, as limited penetration of the drug into the intracranial region was observed.

Introduction

Etoposide is a semisynthetic podophyllotoxin derivative that has been recognized as being efficacious against brain metastasis from lung cancer [7, 13, 15, 18, 24] and germ-cell tumors of the pineal region [14]. It has also been reported to show minor activity against malignant glioma [4–6, 23]. Oral administration of etoposide has recently been demonstrated to be effective in the treatment of several extracranial malignant tumors [1, 8, 22] and intracranial germ-cell tumor [25].

Penetration of etoposide into the intracranial regions, including the brain tumor, after intravenous administration has been revealed pharmacokinetically [16, 17, 20, 21]. However, the extent to which this drug penetrates the brain and cerebrospinal fluid after oral administration remains unclear. It is important that the pharmacokinetics of etoposide after oral dosing be determined in patients exhibiting brain tumors, as the penetration of the drug into the cerebrospinal fluid is known to be extremely poor and because oral administration apparently yields more variable plasma drug concentrations than does intravenous injection. This study is the first to demonstrate the penetration of etoposide into the cerebrospinal fluid following oral dosing. In addition, we pharmacokinetically investigated the appropriate oral dose of etoposide in comparison with its intravenous administration in patients presenting with malignant brain tumors.

Patients and methods

A total of 16 patients, including 10 men and 6 women, who were seen at our institution between May 1989 and September 1990 gave their in-

Offprint requests to: K. Kiya, Department of Neurosurgery, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, Japan

Table 1. Peak concentrations of etoposide in plasma and cerebrospinal fluid

Route	Dose	Patients (*n*)	Peak concentration (μg/ml)	
			Plasma	Cerebrospinal fluid
Intravenous	55 mg/kg	6	7.01 ± 2.89	0.21 ± 0.21
	65 mg/kg	2	10.47 ± 3.43	0.30 ± 0.04
Oral	50 mg	3	1.44 ± 0.33	0.04 ± 0.03
	100 mg	4	4.99 ± 3.14	0.11 ± 0.06
	150 mg	2	3.22 ± 1.40	0.07 ± 0.03

Data represent mean values ± SE

Table 2. Etoposide concentration during surgery at various sites following its intravenous administration to patients presenting with metastatic brain tumors

Patient number	Dose (mg/m^2)	Etoposide Concentration				
		Plasma (μg/ml)	CSF (μg/ml)	Tumor (μg/g)	Necrosis (μg/g)	Brain tissue (μg/g)
1	35	7.7	ND	1.64		ND
2	65	10.7		1.04		0.68
3	65	12.1		2.2		1.34
4	65	13.9	0.04	2.14		0.97
5	90	37.7	ND	4.8	2.92	2.24

All data represented in the table were obtained after end of one infusion. ND, Not detected; CSF, cerebrospinal fluid

Table 3. Penetration ratio of etoposide in cerebrospinal fluid, tumor, or brain tissue

Samples	Patients (*n*)	Penetration ratio (%)[a]
Tumor	5	14.0 ± 2.9
Brain tissue	4	7.4 ± 2.3
Normal CSF	3	0.7 ± 0.5
Pathological CSF[b]	5	3.4 ± 1.0
CSF from the dead space[c]	5	7.2 ± 8.5

Data represent mean values ± SE

[a] Penetration ratios were calculated by dividing the maximal tumor, brain, or cerebrospinal fluid (CSF) concentration by the maximal plasma concentration

[b] Obtained from patients presenting with meningeal carcinomatosis

[c] Aspirated from an Ommaya reservoir placed at the dead space after resection of the tumor

formed consent to participate in this study; their mean age was 48.3 years (range, 17–79 years). In all, 8 subjects presented with metastatic brain tumors, 6 exhibited malignant glioma, 1 displayed a malignant germ-cell tumor, and 1 had malignant lymphoma. Eight patients received intravenous infusions of 55–65 mg/m^2 etoposide (Nippon Kayaku Co. Ltd., Japan) dissolved in 100 ml (0.9%) NaCl solution over 1 h. Blood samples (5 ml) were taken from a peripheral vein prior to the injection and at 1, 2, 3, and 7 h after the start of the infusion. At the same time, 2 ml cerebrospinal fluid was aspirated both from an Ommaya reservoir that had been placed at the anterior horn of the lateral ventricle or dead space following resection of the tumors and from the subarachnoid space by lumbar puncture or from the ventricular drainage. In five patients presenting with metastatic brain tumors, etoposide concentrations in the plasma, cerebrospinal fluid, brain tumor, necrotic tumor, and surrounding brain tissue were determined during the operation following the intravenous administration of 35–90 mg/m^2 etoposide. Approximately 0.5-mg samples were obtained from the various sites at about 1 h after the completion of the infusion. Brain tissue lying ⩾1 cm away from the tumor was obtained during uncapping of the brain that covered the tumor. All plasma, cerebrospinal fluid, tumor, and brain-tissue samples were frozen at –80° C until the etoposide assay.

An oral dose of 50–150 mg etoposide was given daily to nine patients, including five who were treated for 5 consecutive days. Samples of plasma and cerebrospinal fluid were taken before drug administration and at 1, 2, 4, 6, and 24 h thereafter and were prepared in the manner described above. The penetration ratio, i.e., the ratio of etoposide in cerebrospinal fluid, brain tumor, or brain tissue to that in plasma, was calculated using the maximal concentration measured at each site.

Etoposide assay. Drug concentrations in all samples were measured using high-performance liquid chromatography with a fluorescence detector [11]. These samples were added to 4′-demethyl epipodophyllotoxin 9-(4,6-propylidene-β-D-glucopyranoside) as an internal standard. Extraction was performed with chloroform. The chloroform phase was dried under vacuum and then redissolved with 0.25 ml mobile phase [0.02 M KH_2PO_4 CH_3CN(57 : 43, v/v)]. This solution was injected onto a column (Senshu Pak ODS-2251-D) and analyzed with a detector (650-10S, Hitachi Factory, Japan) using an excitation wavelength of 290 nm and a fluorescence wavelength of 320 nm. The flow-rate retention time for this assay was 7.6 min, and the lower limit of detection for etoposide in plasma and tissue was 5 ng/ml and 30 ng/mg, respectively.

Results

Concentration-time curve for etoposide after intravenous administration

Plasma concentrations of etoposide reached a peak at 1 h after end of intravenous infusions of 55 mg/m^2 in six patients (7.01 μg/ml) and of 65 mg/m^2 in two subjects (10.47 μg/ml) as shown in Table 1. In contrast, the drug concentrations in cerebrospinal fluid reached a peak several hours later and were much lower (0.21 and 0.30 μg/ml,

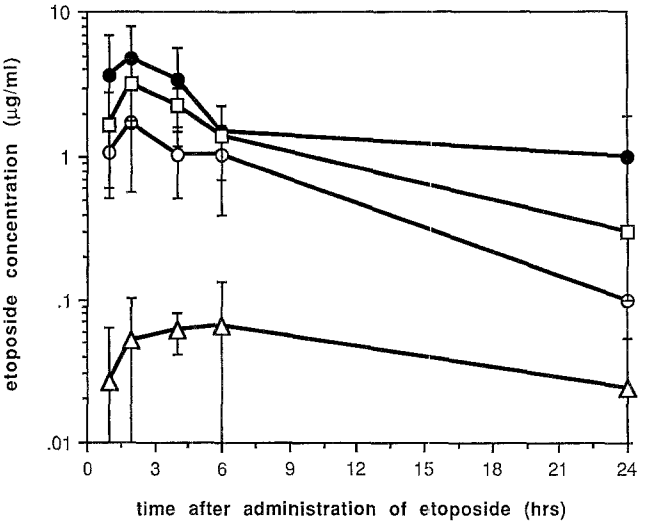

Fig. 1. Plasma and cerebrospinal fluid time-concentration curves after the oral administration of etoposide. The plasma concentration was measured following doses of 50 (○, $n = 3$), 100 (●, $n = 4$), and 150 mg/day (□, $n = 2$); △, cerebrospinal fluid concentration ($n = 6$)

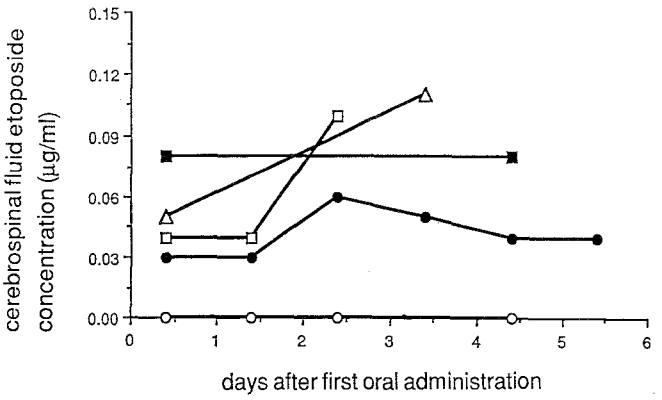

Fig. 2. Cerebrospinal fluid time-concentration curves after the serial oral administration of etoposide. Each point indicates the time-concentration curve calculated for each patient who was treated with 50 (○, ●) or 100 mg/day (□, ■, △)

respectively) than the plasma levels. The peak concentration in both plasma and cerebrospinal fluid corresponded to the injected dose. The areas under the 7-h concentration curves for plasma and cerebrospinal fluid were 30.4 ± 6.7 and 1.56 ± 1.0 μg h ml^{-1}, respectively.

Penetration of etoposide into intracranial regions and cerebrospinal fluid

Table 2 indicates that concentrations of etoposide in the plasma, brain tumor, and brain tissue rose with increasing doses. The mean penetration ratios for brain tumor and brain tissue were 14.0% and 7.4%, respectively (Table 3). Drug concentrations in the cerebrospinal fluid varied, depending on the site from which the samples were drawn and the conditions within the subarachnoid space. The penetration ratio for normal cerebrospinal fluid taken from the ventricular drainage of by lumbar puncture was 0.7%, and that for pathological cerebrospinal fluid obtained from patients suffering from meningeal carcinomatosis was 3.4%. Normal cerebrospinal fluid aspirated from the Ommaya reservoir placed at the dead space after tumor resection showed a penetration ratio of 7.2%.

Concentration-time curve for etoposide after oral administration

Etoposide levels in plasma reached a peak at 2 h after the oral administration of 50, 100, and 150 mg and amounted to 1.44, 4.99, and 3.22 μg/ml, respectively (Table 1, Fig. 1). Drug concentrations in cerebrospinal fluid peaked at 4–6 h after oral doses of 50, 100, and 150 mg and reached levels of 0.04, 0.11, and 0.07 μg/ml, respectively, showing the same pattern as peak plasma levels. Adjustment of the oral dose up to 100 mg resulted in an increase in the peak plasma level, although the absorption of etoposide in each patient apparently also influenced the plasma concentration, especially following a dose of 150 mg. To examine the accumulation of etoposide in the cerebrospinal fluid during serial oral dosing, the drug concentration in cerebrospinal fluid was measured several hours after oral administration during treatment with 50–150 mg etoposide for 5 days. Etoposide did not accumulate in the cerebrospinal fluid despite serial administration (Fig. 2).

Discussion

It has been reported that the penetration of etoposide into the cerebrospinal fluid after intravenous administration to patients presenting with malignant brain tumors is minimal, with a very low concentration of 0–0.13 μg/ml being observed in cerebrospinal fluid following the standard dose of <300 mg/m^2 [2, 23]. In previous studies [5, 9, 10, 12, 17], the etoposide concentration in cerebrospinal fluid was found to remain low, ranging from 0.08 to 1.4 μg/ml, even when higher doses of 300–2500 mg/m^2 had been given intravenously. This poor penetration of etoposide into the cerebrospinal fluid is thought to be attributable to the high binding affinity of the drug to proteins in the blood stream, despite its lipophilic properties [10], which hinders its movement across the blood-brain barrier. As continuous administration of low oral doses of etoposide has been noted to effect a good response in some cancers [8], we used a rather low dose of the drug to investigate its oral administration to patients exhibiting malignant brain tumors. The peak etoposide concentration in the cerebrospinal fluid was found to correspond to the peak plasma level. At the same time, it was also related to the site from which cerebrospinal fluid samples were taken. Etoposide concentrations in the cerebrospinal fluid taken from patients presenting with meningeal carcinomatosis seemed to show slightly higher than those presenting the lesion only within brain parenchymal regions, due to the partial disruption of the blood-brain barrier caused by meningeal carcinomatosis. Moreover, samples of cerebrospinal fluid drawn from the Ommaya reservoir manifested a moderately high drug concentration. It is thought that the wall of the

dead space in which the reservoir is placed contains residual tumor and normal stripped brain tissue and that etoposide distributed in these regions can therefore more readily penetrate into the dead space and be retained in the semiclosed space.

Some investigators have reported on tissue etoposide concentrations. D'Incalci et al. [3] observed that etoposide concentrations in lung metastases and myometrial carcinoma as well as in normal lung tissue and myometrium were much higher than those in subcutaneous tissue. Stewart et al. [21] found that intracerebral tumors contained lower etoposide concentrations than did extracerebral tumors. We detected some etoposide in the brain tumor, which tended to rise with increasing plasma concentrations, as well as a small quantity in the brain tissue, as Lu et al. [16] have also reported. The extent of etoposide penetration into brain tumors and normal brain tissue is apparently lower than that into extracranial tumors and organs, although brain-tumor concentrations are clearly higher than normal brain-tissue levels. The etoposide level in the central necrotic region of the tumor was lower than that in the viable tumor cells at the margin of the tumor, although some investigators [21] have reported contradictory findings.

The pharmacokinetics and the selection of an adequate oral dose of etoposide in patients presenting with malignant brain tumors have not been fully determined [25]. Our results indicate that the plasma concentration is significantly influenced by individual differences in drug absorption from the intestine after oral administration out is approximately one-half of the plasma measured following the intravenous injection of approximately the same dose. In particular, the peak plasma level noted after the oral administration of 150 mg was variable and was lower than that measured after an oral dose of 100 mg; Slevin [19] also failed to find a linear correlation between the oral dose and the plasma drug level. In the present study, the correlation between plasma and metastatic brain-tumor levels was fairly good, suggesting that the oral administration of 100 mg etoposide in clinical trials in patients exhibiting malignant brain tumors is warranted. Serial oral administration may also be useful, as the cytotoxic effect of etoposide is partially augmented by time-dependent dosing [8] and no accumulation was demonstrated even in the cerebrospinal fluid after serial dosing.

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