SHORT COMMUNICATION

Pharmacokinetics of Low Dose Etoposide after Multiple Oral Administration

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Etoposide has a broad spectrum against solid tumors¹⁾ as well as hematological malignancies.²⁾ Early preclinical study demonstrated that daily administration for five consecutive days or intermittent administration at two- to four-day intervals was superior to intermittent administration at six- to eight-day intervals in mice with L 1210 leukemia.³⁾ Although Hainsworth et al. have recently reported a phase 1 trial of oral daily administration of low dose etoposide,⁴⁾ pharmacokinetic analysis was, unfortunately, not performed.

The aims of this work are (i) to report the pharmacokinetics of oral low dose etoposide and (ii) to compare the kinetic parameters after the first dosing with those after repeated dosing.

Patients and Methods

After informed consent had been obtained, 4 patients (Patient A, lung cancer, 40 yr, 58 kg; Patient B, lung cancer, 70 yr, 44 kg; Patient C, lung cancer, 47 yr, 44 kg; Patient D, breast cancer, 47 yr, 72 kg) and 3 patients (Patient E, lung cancer, 40 yr, 38 kg; Patient F, lung cancer, 70 yr, 43 kg;

Patient G, lung cancer, 36 yr, 43 kg), who were admitted to Nagoya Memorial Hospital, received etoposide (Lastet ®25, Nippon Kayaku Co., Ltd., Tokyo, Japan) orally in the morning before breakfast for 7 consecutive days at doses of 25 mg and 50 mg (25 mg cap. × 2), respectively. Any other chemotherapy had been finished more than 6 wk before the enrollment in the study. No signs of renal and/or hepatic damage were observed over this protocol. During this trial, all administrations of etoposide were executed and no G. I. troubles which might affect the absorption of this drug were found. On days 1 and 7, peripheral blood sampling (5 ml each) was performed at 0, 0.5, 1, 2, 4, 8, 10 and 24 hr after administration. Plasma etoposide concentrations were assayed by HPLC method as described recently.⁵⁾

Unweighed plasma concentration data after an oral etoposide administration were fitted to one-compartment open model.⁶⁾ The best fitting various pharmacokinetic parameters were calculated by the iterative non-linear least squares computer program, MULTI⁷⁾, adapted for a microcomputer FM-16 β (Fujitsu Co., Ltd., Tokyo, Japan). All data are presented as means $\pm$ S. D. Statistical comparisons were performed using one-way analysis of variance.

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Results and Discussion

Figure 1 illustrates the mean serum levels of etoposide on days 1 and 7 after administrations of 25 and 50 mg. The observed maximum concentrations after 25 and 50 mg were 1.50 ± 0.81 and $3.21 \pm 0.95 \mu\text{g/ml}$, respectively, on day 7. The minimum concentrations at 24 hr after the respective doses were 0.13 ± 0.08 and $0.20 \pm 0.14 \mu\text{g/ml}$, respectively, on day 7. There was a proportional increase of concentration in accordance with the dosage increment. The pharmacokinetic data analyzed by one-compartment model are summarized

in Tab. 1. Although K_a showed large inter- and intraindividual variations, K_{el} was revealed to be relatively stable within the same individual but largely varied among subjects. The value of V_d/F seems to be larger in the low dose study as compared to the high dose study. This is because Patient A in the low dose study had V_d/F of around 0.7 l/kg , which was three times larger than those of the others. Because this patient was not fat, this may result from constant but incomplete absorption of etoposide at this dose. Although clearance/F ranged from 0.023 to 0.111 l/hr/kg throughout the studies, the mean intra-individual difference of clear-

Fig. 1 Plasma concentration of etoposide on days 1 and 7 at a 25 mg dose and a 50 mg dose. Data are presented as means $\pm$ S. D.

Tab. 1 Pharmacokinetic Parameters of Etoposide after Oral Consecutive Administration at 25 or 50 mg Dose

Parameter	Dose			
	25 mg (n=4)		50 mg (n=3)	
	day 1	day 7	day 1	day 7
K_a (h^{-1})	4.673 ± 4.692	7.533 ± 8.985	16.314 ± 5.693	7.492 ± 10.04
K_{el} (h^{-1})	0.163 ± 0.042	0.145 ± 0.045	0.165 ± 0.062	0.188 ± 0.045
V_d/F (l/kg)	0.340 ± 0.217	0.345 ± 0.267	0.377 ± 0.098	0.266 ± 0.092
Lag time to absorption (hr)	0.413 ± 0.417	0.018 ± 0.018	0.137 ± 0.308	0.012 ± 0.041
Clearance/F (l/hr/kg)	0.055 ± 0.038	0.048 ± 0.037	0.061 ± 0.028	0.049 ± 0.017

There was no significant difference in the parameters by ANOVA.

ance/F was 0.010 ± 0.008 l/hr/kg. Thus, the parameter, which is considered the most important in calculating the dosage regimen, was rather constant in the same patient, independently of dose and time after dosing. In view of these data, it could be concluded that neither accumulation nor alteration of absorption was observed with repeated administrations of very low dose etoposide.

In contrast, Harvey et al. showed that inter-patient coefficients of variation after oral administration of 400 mg once a day for three successive days ranged over 19-45% for the peak concentration and 16-53% for the area under the concentration-time curve⁸⁾. This may be due to the non-linear bioavailability of oral etoposide above 200 mg⁹⁾, but there is little understanding as to why such inter-patient variation occurs.

Since etoposide is eliminated via both hepatic and renal route, there were significant correlations between plasma clearance and renal or hepatic function.¹⁰⁾ In the present study with lower doses of etoposide, we have shown that the clearance/F within the same individual is relatively stable with repeated dosings when renal and/or hepatic dysfunctions are not observed. If the kinetic parameter might change in the same subject, attention should be paid to the dosage regimen of oral etoposide even in low dose regimen. Our finding may lead to a new dosage regimen in cancer therapy.

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References

- 1) Evans, W. K., Shepherd, F. A., Feld, R. et al.: VP-16 and cisplatin as first-line therapy of small-cell lung cancer. *J. Clin. Oncol.*, **3**: 1471-1477 (1985).
- 2) Stahlein, H.: Activity of a new glycosidic lignan derivative (VP-16-213) related to podophyllotoxin in experimental tumors. *Eur. J. Cancer*, **9**: 215-221 (1973).
- 3) Dombernowsky, P. and Nissen N. I.: Schedule dependency of the antileukemic activity of the podophyllotoxin-derivative VP-16-213 (NSC-141540) in L1210 leukemia. *Acta Pathol. Microbiol. Scand.*, [A] **81**: 715-724 (1973).
- 4) Hainsworth, J. D., Johnson, D. H., Fraizier, S. R. et al.: Chronic daily administration of oral etoposide—1 phase 1 trial. *J. Clin. Oncol.*, **7**: 396-401 (1989).
- 5) Idzu, G., Yazawa, Y., Tachikawa, M. et al.: Determination of etoposide in plasma by high performance liquid chromatography with fluorescence detection. *Kiso to Rinsyo*, **23**: 479-484 (1989) (in Japanese).
- 6) Gibaldi, M. and Perrier, D.: *Pharmacokinetics*, Marcel Dekker, New York, pp. 97-128 (1975).
- 7) Yamaoka, K., Tanigawara, Y., Nakagawa, T. et al.: A pharmacokinetic analysis program (MULTI) for microcomputer. *J. Pharmacobiodyn.*, **4**: 879-885 (1981).
- 8) Harvey, V. J., Slevin, M. L., Joel, S. P. et al.: Variable bioavailability following repeated oral doses of etoposide. *Eur. J. Cancer Clin. Oncol.*, **21**: 1315-1319 (1985).
- 9) Harvey, V. J., Slevin, M. L., Joel, S. P. et al.: The effect of dose on the bioavailability of oral etoposide. *Cancer Chemother. Pharmacol.*, **16**: 178-181 (1986).
- 10) Clark, P. I. and Slevin, M. L.: The clinical pharmacology of etoposide and teniposide. *Clin. Pharmacokinet.*, **12**: 223-252 (1987).