

Inter- and Inpatient Variability in Etoposide Kinetics with Oral and Intravenous Drug Administration¹

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ABSTRACT

The objective of this study was to accurately determine the within- and between-patient variability in etoposide pharmacokinetics for i.v. and p.o. administered drug. Inter- and inpatient variability in systemic etoposide exposure was measured following i.v. and p.o. drug administration using stable isotope dilution methodology. Seven patients received 50 mg of etoposide by both p.o. and i.v. routes of administration on three separate occasions 1 month apart. Etoposide plasma concentrations following p.o. and i.v. drug administration were quantitated by liquid chromatography-mass spectrometry for each route of administration. The area under the plasma etoposide concentration *versus* time curve, plasma etoposide clearance, and etoposide plasma half-life were calculated for each dose of drug. Kinetic measurements following i.v. and p.o. drug administration were compared. The within-patient variation in the areas under the plasma etoposide concentration *versus* time curves following i.v. drug administration was minimal [coefficient of variation (CV) = 9.3%]. Within-patient variability was increased 2.4-fold with oral drug administration (inpatient CV = 22.2%). Between-patient variability was roughly three times as great as within-patient variability (interpatient i.v. CV = 28.4%; interpatient p.o. CV = 58.3%). Mean etoposide bioavailability at a dose of 50 mg was 64.6%, again with greater interpatient than inpatient variability (34.8 *versus* 22.6%). Greater variation in drug toxicity is expected with p.o. compared with i.v. etoposide use. Administration of repeated doses of etoposide to the same patient should produce less variation in toxicity than between-patient dosing.

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³ The abbreviations used are: AUC, area under the concentration *versus* time curve; CV, coefficient of variation; GI, gastrointestinal; D₄-etoposide, deuterated etoposide; D₀-etoposide, nondeuterated etoposide.

INTRODUCTION

Toxicity resulting from use of an antineoplastic agent is generally related to total systemic drug exposure as described by the AUC (1, 2). This has been demonstrated for etoposide. Several studies have documented a direct correlation between systemic exposure (AUC) from a given dose of etoposide and the degree of treatment-related myelosuppression (3–6). Variability in how individual patients absorb etoposide into plasma and clear drug from the systemic circulation may account for a significant component of differences in toxicity. Pharmacokinetic variability may result from day-to-day changes in an individual patient's ability to metabolize or excrete etoposide or from between-patient differences in drug metabolism or excretion.

Etoposide is available as i.v. and p.o. preparations. Oral etoposide bioavailability has been measured as 40–75% (7–10). This means that the AUC of a given oral dose is only 40–75% of what would be achieved after an i.v. dose. Giving a higher dose p.o. than would be given i.v. can compensate for low oral bioavailability. However, p.o. administration may increase the variability in the AUC achieved with a given dose of drug because the drug must undergo the additional processes of being transported across the intestine, passing through the liver, and entering the systemic plasma circulation. Increased variability in systemic exposure will likely lead to greater variability in toxicity and antineoplastic activity.

The degree of variation in systemic drug exposure is best represented by the CV (the ratio of the SD to the mean) of the AUC seen in a group of patients (11). A large CV for a patient population suggests that some patients are receiving an inadequate drug exposure, resulting in suboptimal tumor cytotoxicity, whereas another percentage of the treated population is receiving an AUC causing excess toxicity. In the current study, we administered etoposide p.o. and i.v. on three occasions to a series of patients to quantitate intra- and inter-patient variability in both the i.v. and the p.o. AUC. To eliminate the day-to-day inpatient variability in comparisons of p.o. and i.v. drug administration, a stable-isotope technique was used, allowing simultaneous administration of p.o. and i.v. drug to the same patient.

PATIENTS AND METHODS

Patients. Cancer patients receiving etoposide as part of their chemotherapy regimen participated in these pharmacokinetic studies. All patients had a WHO performance status of 0–2 and histologically proven malignancy. Their disease could not involve the GI tract. No immunoadjuvants or radiation were given within 4 weeks preceding the study or chemotherapy given within the previous 14 days. Patients had recovered from the toxic effects of previous treatment. Patients had WBC counts $\geq 3,000/\text{mm}^3$, platelet counts $\geq 100,000/\text{mm}^3$, blood urea nitrogen ≤ 25 mg/dl, serum creatinine $\leq 1.5 \times$ normal, lactate dehy-

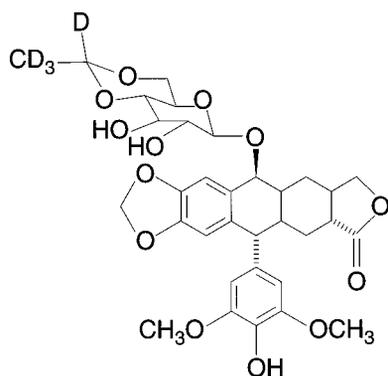


Fig. 1 Structure of deuterated etoposide.

drogenase $\leq 1.5 \times$ normal, alkaline phosphates $\leq 1.5 \times$ normal, and glucose ≤ 200 mg/dl before each of the study days. All patients had a negative stool guaiac test prior to entry into the study. Patients were excluded if they had any GI condition that could interfere with drug absorption, including active ulcers, recurring diarrhea, or GI resection. Patients were excluded if they had an acute infection, were using aminoglycosides, diuretics, antacids, H_2 antagonists, caffeine, alcohol, or any medication affecting GI absorption during the week prior to study. These agents were not given during the 24-h monitoring period. Patients were admitted to the Vanderbilt Clinical Research Center 14 h before drug dosing and remained for 24 h after dosing. No other chemotherapeutic drugs were given for 2 weeks preceding or during the plasma sampling period. All patients signed an informed consent approved by the Vanderbilt Institutional Review Board prior to their participation in pharmacokinetic studies.

For studies evaluating the deuterium isotope effect, six patients with lung cancer and one patient with non-Hodgkin's lymphoma were studied. All had serum albumin concentrations > 3.0 g/dL prior to evaluation. Three patients had received no previous chemotherapy, and three had received one previous treatment regimen. For studies comparing variability in p.o. and i.v. drug administration, five patients with lung cancer, one with leiomyosarcoma, and one with hepatocellular cancer were studied. All patients had a serum albumin concentration > 3.0 g/dL prior to each treatment, with the exception of patient 2, who had serum albumin values of 2.3, 2.7, and 3.1 g/dL prior to each treatment cycle. Three patients had received no prior chemotherapy, two patients had received one prior regimen, and two patients had received two prior chemotherapeutic regimens.

Etoposide Formulation. Deuterated (D_4) etoposide was synthesized by Bristol-Myers Squibb (Princeton, NJ; Fig. 1). Deuterated etoposide powder contained 79.7% D_4 -etoposide, 12.4% D_3 -etoposide, 3.1% D_2 -etoposide, 1.0% D_1 -etoposide, and 2.7% D_0 -etoposide as verified by mass spectrometry. Standard etoposide (D_0) was supplied as a 5-ml solution containing 20 mg D_0 -etoposide/ml. Three oral formulations of oral etoposide were used because this study was initially designed to compare bioavailability of different oral etoposide preparations. One oral formulation contained 50 mg of etoposide commercially available as Vepesid capsules (Bristol-Meyers/Squibb, Princeton,

NJ). Other preparations were 25- and 50-mg capsules reformulated to eliminate the need for refrigeration.

Pharmacokinetic Sampling and Analysis. Blood samples (7 ml) were collected in Vacutainer tubes containing potassium EDTA at 0, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h after etoposide dosing was started. After collection, the tubes were gently inverted to ensure thorough mixing with the anticoagulant and immediately placed on ice. The samples were centrifuged within 1 h of collection at $1000 \times g$ for 15 min. A minimum of 3 ml of plasma was stored at or below 20°C . Quality control samples with added D_0 -etoposide and D_4 -etoposide were stored with the study samples until analysis. Concentrations of D_0 - and D_4 -etoposide in plasma samples, quality control samples, and dosing solutions were determined by ion spray liquid chromatography-mass spectrometry methodology. Podophyllotoxin was used as an internal standard with solid phase extraction. Standard curves were linear over a concentration range of 5–1000 ng/ml for D_0 - and D_4 -etoposide with coefficients of regression ≥ 0.997 . The between- and within-day CVs for D_0 -etoposide were $< 7\%$ and $< 11\%$, respectively. For D_4 -etoposide, the between- and within-day CVs were $< 5\%$ and $< 10\%$, respectively. Mean predicted concentrations of the quality control samples were within 14% of the nominal values for both D_0 - and D_4 -etoposide over a range of 5–1000 ng/ml. The reproducibility of the storage quality control demonstrated etoposide stability during sample storage.

Plasma concentration-time data were analyzed by noncompartmental methods (12). The terminal log-linear portion of each plasma profile was identified by linear regression of the data points, which minimized the mean square error, and then the terminal elimination rate constant, K , was derived from the absolute value of the slope of this log-linear phase. The elimination half-life was determined from the relationship: $T_{1/2} = 0.693/K$. The area under the plasma concentration-time curve from 0 to infinity was determined by a combination of the trapezoidal and long-trapezoidal methods, with extrapolation to infinity. Bioavailability (F) was determined from the ratio of the etoposide AUC achieved after oral (D_0) administration divided by the etoposide AUC achieved following i.v. (D_4) administration. Because etoposide exhibits linear kinetics after i.v. administration (13, 14), c_{MAX} and AUC values were normalized to a 50-mg dose prior to statistical analysis. Paired t tests were used to compare the pharmacokinetic parameters. ANOVA with Dunnett's correction was used for multiple comparisons.

Study Designs. To assure that the disposition of labeled (D_4) drug was similar to unlabeled drug, 50 mg of deuterated (D_4) etoposide and 50 mg of unlabeled (D_0) etoposide (total etoposide dose, 100 mg) were administered simultaneously by the i.v. route to six patients. Each patient received 250 ml of a dosing solution containing 0.2 mg/ml D_0 -etoposide and 0.2 mg/ml D_4 -etoposide (50 mg of D_0 -etoposide plus 50 mg of D_4 -etoposide) as a 1-h constant-rate i.v. infusion using a calibrated infusion pump. Plasma sampling was performed prior to and following termination of the 1-h infusion.

To evaluate intra- and interpatient variability in systemic exposure to etoposide given by both i.v. and p.o. administration, seven patients were simultaneously given 50 mg of unlabeled (D_0) etoposide p.o. and 50 mg of deuterated (D_4) etoposide i.v. on three separate occasions separated by 1 month (total etopo-

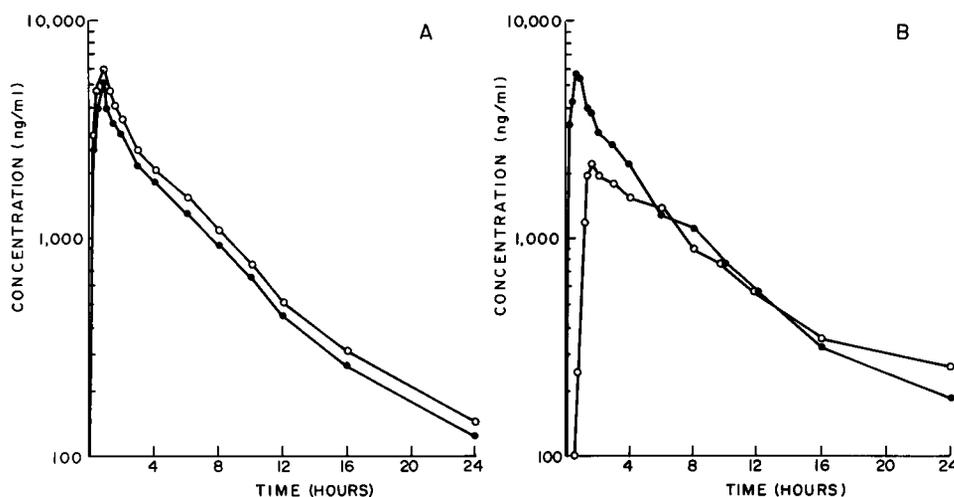


Fig. 2 A, Plot of etoposide concentration versus time after drug administration for a single patient receiving 50 mg of D₀-etoposide i.v. and 50 mg of D₄-etoposide i.v. B, similar plot from a patient receiving 50 mg of D₄-etoposide i.v. and 50 mg of D₀-etoposide p.o. ●, D₄-etoposide; ○, D₀-etoposide.

side dose, 100 mg at each treatment). All seven patients received each of the following treatments: treatment 1, 50 mg of deuterated (D₄) etoposide by 1-h i.v. infusion and 50 mg of unlabeled (D₀) etoposide p.o. as a 50-mg marketed Vepesid capsule at the start of the infusion; treatment 2, 50 mg of deuterated (D₄) etoposide by 1-h i.v. infusion and 50 mg of unlabeled (D₀) etoposide p.o. as a 50-mg reformulated capsule at the start of the infusion; treatment 3, 50 mg of deuterated (D₄) etoposide by 1-h i.v. infusion and 50 mg of unlabeled (D₀) etoposide p.o. given as two 25-mg reformulated capsules at the start of the infusion. The sequence of treatments was determined randomly. The deuterated etoposide (250 ml of a 0.2 mg/ml solution) was administered as a 60-min infusion using pediatric i.v. tubing and a calibrated infusion pump. Oral capsules were administered with 200 ml of water at the time of the start of infusion. Patients fasted for 10 h prior to drug dosing and for 3 h after dosing. Serial blood samples were obtained prior to and for 24 h after the start of the infusion.

RESULTS

Deuterium Isotope Effect. The use of stable isotopes for bioavailability/bioequivalence testing is based on the assumption that the introduction of the stable isotope label does not alter the kinetics of a drug. However deuterium, because of a 2-fold difference in mass from hydrogen and its extensive involvement in metabolic reactions, has been known to exert a significant effect on the pharmacokinetics of some drugs (15). To investigate the presence or absence of isotopic effects on the disposition of etoposide, six patients received D₀ and D₄ simultaneously by i.v. infusion (Fig. 2A). The mean maximal D₀- and D₄-etoposide plasma concentrations and etoposide AUC values were comparable in these six patients (Table 1). The median time to maximal drug concentration was 1 h for both treatments and corresponded to the end of the i.v. infusion. The mean half-life, clearance, *c*_{MAX}, and *V*_{dis} (volume of distribution at steady state) values for D₀- and D₄-etoposide were similar (Table 1). No significant difference in any pharmacokinetic parameter was noted. These results indicate no isotope effect on the disposition of i.v. deuterated etoposide.

Table 1 Etoposide kinetics following simultaneous i.v. administration of D₀- and D₄-etoposide (*n* = 6)

	D ₀	D ₄	<i>P</i>
AUC (ng/ml × h)	32,699 ± 8,779	33,347 ± 9,616	0.17
Clearance (ml/min/m ²)	14.68 ± 4.03	14.48 ± 4.03	0.12
<i>c</i> _{MAX} (ng/ml)	5,232 ± 922	5,288 ± 994	0.38
Half-life (h)	7.70 ± 1.53	7.71 ± 1.78	0.93

Effect of Oral Etoposide Formulations on Pharmacokinetics. The effect on drug absorption, metabolism, and excretion by the different oral formulations of etoposide used in this study was evaluated by comparing the etoposide bioavailability and plasma half-life measured after administration of each preparation (Table 2). The bioavailability achieved after administration of each preparation for each patient is shown in Fig. 3. No consistent trend is noted for a higher bioavailability for any specific preparation. Although the power of the study is not great enough to statistically conclude that the three formulations are identical, no differences can be measured.

Intra- and Interpatient Variability in p.o. and i.v. Administered Etoposide. Assuming that the p.o. etoposide formulations are similar, our study design allowed an opportunity to compare within- and between-patient variability in etoposide AUC with both p.o. and i.v. administered drug. Seven patients received 50 mg of D₄-etoposide i.v. and 50 mg of D₀-etoposide p.o. simultaneously on three separate occasions 1 month apart (Fig. 2B). The mean AUC achieved after p.o. administration of 50 mg of etoposide in all 21 studies was 17,948 ± 9,943 ng/ml × h. The mean AUC achieved after administration of 50 mg of i.v. etoposide was 26,752 ± 7,424 ng/ml × h. The mean half-life (± SD) for p.o. and i.v. administered drug was 7.8 ± 2.7 and 7.0 ± 2.9 h, respectively. Mean clearance values for p.o. and i.v. administered drug were 58.1 ± 25.2 ml/min and 31.5 ± 10.4 ml/min, respectively. The AUCs achieved following all 21 administrations of i.v. and p.o. etoposide are shown in Tables 3 and 4.

The effect of route of administration on inpatient variability was calculated by determining of CV (SD/mean) in the

Table 2 Etoposide kinetics following administration of 50 mg in different oral formulations ($n = 7$)

	Formulation			P		
	1	2	3	1 vs. 2	1 vs. 3	2 vs. 3
Bioavailability (%)	61.5 ± 27.6	71.7 ± 16.5	64.2 ± 18.0	NS ^a	NS	NS
T_{MAX} (h)	1.96 ± 1.35	1.33 ± 1.25	0.94 ± 0.34	NS	NS	NS
Half-life (h)	7.41 ± 1.10	7.78 ± 2.49	8.25 ± 4.05	NS	NS	NS

^a NS, not significant.

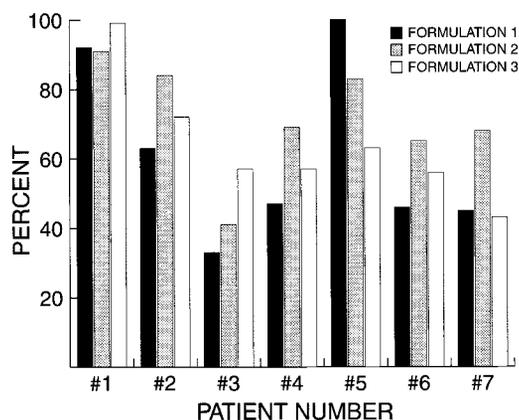


Fig. 3 Etoposide bioavailability seen with different 50-mg etoposide formulations administered to the seven study patients.

Table 3 AUC (ng/ml × h) following administration of 50 mg of etoposide i.v. on three separate occasions to seven patients

Patient	Course			CV (%)
	1	2	3	
1	41,634	41,830	41,878	0.7
2	26,940	25,512	25,093	3.7
3	23,300	22,764	26,196	7.7
4	34,293	25,235	29,764	15.2
5	19,638	25,551	18,303	18.2
6	22,716	24,721	27,558	9.7
7	20,859	18,342	22,379	9.9
CV (%)	29.8	27.9	27.5	

AUC seen with both i.v. and p.o. administered drug for all seven patients (Tables 3 and 4). The average inpatient variability with p.o. administration (22.2%) was roughly twice as great as with i.v. administration (9.3%; $P = 0.017$). Between-patient variability was greater for both routes of administration (58.2 and 28.4%, respectively). Mean etoposide bioavailability was similar when measured within the same patient or between patients (65 versus 65%). However, between-patient variation in bioavailability was greater than within-patient variability (CV = 34.8 versus 22.6%; $P = 0.005$). No significant improvement in variability was noted when dose was adjusted for the patient's body surface area.

DISCUSSION

Oral administration of an antineoplastic agent has potential advantages (16). It is convenient with no needle punctures or

Table 4 AUC (ng/ml × h) following administration of 50 mg of etoposide orally on three separate occasions to seven patients

Patient	Course			CV, %
	1	2	3	
1	38,150	37,942	42,202	6.1
2	16,845	21,529	18,092	12.9
3	7,618	9,397	15,004	36.1
4	15,939	17,338	9,397	29.8
5	21,122	21,232	11,641	30.6
6	10,373	16,133	15,524	22.5
7	9,265	12,540	9,647	17.1
CV, %	61.4	47.6	65.8	

requirement of a nurse or physician for administration. However, oral use adds the processes of intestinal drug uptake with transport of active compound through the hepatic system to plasma. These processes may increase pharmacokinetic variability. Wide variability in absorption may result in suboptimal antitumor activity in some patients, whereas other patients may be at risk for excess toxicity. This study attempts to quantify the effect of route of drug administration on the day-to-day within- and between-patient variability in systemic exposure achieved with a given etoposide dose.

By using deuterated etoposide as an i.v. preparation, day-to-day variation in etoposide clearance is eliminated. An accurate comparative measurement of the variability produced by the route of drug administration can, therefore, be quantitated. This is the only study measuring variability in etoposide bioavailability that uses stable isotope dilution methodology. Repeated simultaneous administration of the same dose of p.o. and i.v. drug to the same group of patients allows measurement of inter- and inpatient variability. Potential confounding factors in this study are the use of three different oral etoposide preparations and use of deuterated etoposide. However, our results indicate that deuterated etoposide behaves similarly to nondeuterated drug. Our results also suggest no difference in bioavailability among the oral drug preparations used. If one assumes the different formulations to be similar and that deuterated and nondeuterated drug are similar, this study allows precise assessment of the effect of day-to-day variation in clearance, both within and between patients, and the effect of the route of drug administration on variability.

Other studies have evaluated the variability in clearance or AUC achieved from a given dose of etoposide (Table 5), although not with use of the stable isotope methodology. The measurement of the between-patient variation in AUC (or clearance) for i.v. administered etoposide has ranged from 7 to 49%

Table 5 Variability in etoposide clearance in published studies

Study	Patients	Administration	Inter- or Inpatient	Clearance (ml/min/m ²)	CV (%)
Creaven and Allen (17)	9	i.v.	Inter	17.6	30
D'Incalci <i>et al.</i> (18)	14	i.v.	Inter	26.8	7
Hande <i>et al.</i> (13)	12	i.v.	Inter	28.0	35
Stewart <i>et al.</i> (19)	10	i.v.	Inter	24.9	36
Arbuck <i>et al.</i> (20)	17	i.v.	Inter	21.9	37
Bennett <i>et al.</i> (21)	17	i.v.	Inter	24.5	49
Lowis <i>et al.</i> (22)	33	i.v.	Inter	26.0	33
Hande <i>et al.</i> (8)	11	Oral	Inter	37.7	39
Millward <i>et al.</i> (24)	15	Oral	Inter	35.2	45
Fujiwara <i>et al.</i> (10)	9	Oral	Inter	18.9	15
Joel <i>et al.</i> (9)	10	Oral	Inter	NA ^a	35
deJong <i>et al.</i> (25)	17	Oral	Inter	31.4	48
Zuchetti <i>et al.</i> (23)	22	Oral	Inter	29.7	39
Ratain <i>et al.</i> (3)	21	i.v.	Intra	21.5	15
Lowis <i>et al.</i> (22)	11	i.v.	Intra	NA	12
Harvey <i>et al.</i> (26)	7	Oral	Intra	39.8	30
Zuchetti <i>et al.</i> (23)	9	Oral	Intra	NA	17

^a NA, not applicable.

(mean, 31%). For oral drug, measured variations in clearance have been slightly greater but with a wide range of values (range, 15–48%; mean, 37%). Within-patient variability in etoposide clearance has been studied less frequently. However, the CV from dose to dose has been significantly less within the same patient compared with measurements taken between patients. Our study confirms that the within-patient variability in drug clearance for i.v. administered drug is small (9.3%). Variability is increased 3-fold with oral administration (28.4%). Between-patient variability is twice as great as within-patient variability for both i.v. and p.o. administered drug.

Relatively few antineoplastic agents can be administered by both i.v. and oral routes (16). Increased variability in systemic drug exposure after oral drug administration has been noted with several of these antineoplastic agents. In studies by Campbell *et al.* (27) and Oguey *et al.* (28), interpatient variability in methotrexate clearance roughly doubled (2.2- and 1.7-fold) when drug was given by the p.o. rather than the i.v. route. Similarly, the CV in the AUC following 6-mercaptopurine administration was found to be greater for p.o. than i.v. administered drug (CV, 60 versus 49%; Ref. 29). Juma *et al.* (30) found greater variability in the AUC achieved after p.o. cyclophosphamide administration than with i.v. drug use (55 versus 29%), a result not confirmed by Struck *et al.* (31). Our study adds to the general trend that the oral route of administration of an antineoplastic agent adds to pharmacokinetic variability.

The specific reason for the increased pharmacokinetic variability with p.o. administered etoposide is not known. It may result from patient-to-patient differences in the rate of drug uptake through the GI mucosa or from differences in first-pass hepatic drug metabolism. Etoposide is glucuronidated by the liver and metabolized oxidatively (32). However, its hepatic clearance rate is not high (33); therefore, variation in hepatic metabolism is not likely to explain differences between p.o. and i.v. drug administration. Etoposide is poorly soluble in water. Variability in absorption may be related to its instability in gastric or intestinal solutions. Etoposide is transported by p-glycoprotein and metabolized by cytochrome P450 3A4, two

proteins found in the brush-border membrane of the small intestine (34, 35). It is possible that changes in intestinal P-glycoprotein or 3A4 concentrations may contribute to variable intestinal uptake of drug (16).

In summary, this study, in which p.o. and i.v. etoposide were given simultaneously to a group of patients on repeated occasions, shows that within-patient variability in the systemic etoposide exposure is modest with i.v. administered drug. The oral route of administration triples variability. Between-patient variability is twice as great as within-patient. Because many studies have shown that toxicity is directly related to the etoposide AUC achieved, greater variability in etoposide toxicity would be expected between patients than with a repeated dose to the same patient. The oral route of drug administration is also likely to increase variability in toxicity.

REFERENCES

1. Kobayashi, K., Jodrell, D. I., and Ratain, M. J. Pharmacodynamic-pharmacokinetic relationships and therapeutic drug monitoring. *Cancer Surveys*, 17: 51–78, 1993.
2. Galpin, A. J., and Evans, W. E. Therapeutic drug monitoring in cancer management. *Clin. Chem.*, 39: 2419–2430, 1993.
3. Ratain, M. J., Mick, R., Schilsky, R. L., Vogelzang, N. J., and Berezin, F. Pharmacologically based dosing of etoposide: a means of safely increasing dose intensity. *J. Clin. Oncol.*, 9: 1480–1486, 1991.
4. Stewart, C. F., Arbuck, S. G., Fleming, R. A., and Evans, W. E. Relationship of systemic exposure to unbound etoposide and hematologic toxicity. *Clin. Pharmacol. Ther.*, 50: 385–393, 1991.
5. Joel, S. P., Shah, R., Clark, P. T., and Slevin, M. L. Predicting etoposide toxicity: relationship to organ function and protein binding. *J. Clin. Oncol.*, 14: 257–267, 1996.
6. McLeod, H. L., and Evans, W. E. Clinical pharmacokinetics and pharmacodynamics of epipodophyllotoxins. *Cancer Surveys*, 17: 253–267, 1993.
7. Smith, R. D., Pfeffer, M., Scalzo, A., and Comis, R. L. Bioavailability and pharmacokinetics of etoposide. *Semin. Oncol.*, 12 (Suppl.): 48–51, 1985.
8. Hande, K. R., Krozely, M. G., Greco, F. A., Hainsworth, J. D., and Johnson, D. H. Bioavailability of low-dose etoposide. *J. Clin. Oncol.*, 11: 374–377, 1993.

9. Joel, S. P., Clark, P. I., Heap, L., Webster, L., Robbins, S., Craft, H., and Slevin, M. L. Pharmacological attempts to improve the bioavailability of oral etoposide. *Cancer Chemother. Pharmacol.*, *37*: 125–133, 1995.
10. Fujiwara, Y., Ohune, T., Okusaki, K., Niitani, K., Sumiyoshi, H., Taakemoto, Y., Yamaoka, N., and Yamkido, M. Bioavailability of 50 and 75 mg oral etoposide in lung cancer patients. *Cancer Chemother. Pharmacol.*, *37*: 327–331, 1996.
11. Ratain, M. J. Pharmacokinetics and pharmacodynamics. In: V. T. DeVita, S. Hellman, and S.A. Rosenberg (eds.), *Cancer: Principles and Practice of Oncology*, Ed. 5, pp. 375–385. Philadelphia, PA: Lippincott-Raven, 1997.
12. Gibaldi, M., and Perrier, D. *Pharmacokinetics*, Ed. 2, pp. 1–9C. New York, NY, Marcel Dekker, 1982.
13. Hande, K. R., Wedland, P. J., Noone, R. M., Wilkinson, G. R., Greco, F. A., and Wolff, S. N. Pharmacokinetics of high-dose etoposide (VP-16-213) administered to cancer patients. *Cancer Res.*, *44*: 379–382, 1984.
14. Newman, E. M., Doroshow, J. H., Forman, S. J., and Blume, K. G. Pharmacokinetics of high-dose etoposide. *Clin. Pharmacol. Ther.*, *43*: 561–564, 1988.
15. Devlin, R., Cohen, A., Funke, P., and Stern, M. Stable isotopes in bioequivalence testing. *Clin. Pharmacol. Ther.*, *31*: 217–218, 1982.
16. DeMario, M. D., and Ratain, M. J. Oral chemotherapy: rationale and future directions. *J. Clin. Oncol.*, *16*: 2557–2567, 1998.
17. Creaven, P. J., and Allen, L. M. EPEG, a new antineoplastic epipodophyllotoxin. *Clin. Pharmacol. Ther.*, *10*: 221–226, 1975.
18. D'Incalci, M., Farina, P., Sessa, C., Mangioni, C., Conter, V., Maserà, G., Rocchetti, M., Pisoni, M. B., Piazza, E., Beer, M., and Cavalli, F. Pharmacokinetics of VP16-213 given by different administration methods. *Cancer Chemother. Pharmacol.*, *7*: 141–145, 1982.
19. Stewart, D. J., Nundy, D., Maroun, J. A., Tetreault, L., and Prior, J. Bioavailability, pharmacokinetics and clinical effects of an oral preparation of etoposide. *Cancer Treat. Rep.*, *69*: 269–273, 1985.
20. Arbus, S. G., Douglas, H. O., Crom, W. R., Goodwin, P., Silk, Y., Cooper, C., and Evans, W. E. Etoposide pharmacokinetics in patients with normal and abnormal organ function. *J. Clin. Oncol.*, *4*: 1690–1695, 1986.
21. Bennett, C. L., Sinkule, J. A., Schilsky, R. L., Senekjian, E., and Choi, K. E. Phase I clinical and pharmacological study of 72-hour continuous infusion of etoposide in patients with advanced cancer. *Cancer Res.*, *47*: 1952–1956, 1987.
22. Lewis, S. P., Pearson, A. D. J., Newell, D. R., and Cole, M. Etoposide pharmacokinetics in children: the development and prospective validation of a dosing equation. *Cancer Res.*, *53*: 4881–4889, 1993.
23. Zucchetti, M., Pagani, O., Torri, V., Sessa, C., D'Incalci, M., DeFusco, M., deJong, J., Gentilli, D., Martinelli, G., Tinazzi, A., and Cavalli, F. Clinical pharmacology of chronic oral etoposide in patients with small cell and non-small cell lung cancer. *Clin. Cancer Res.*, *1*: 1517–1524, 1995.
24. Millward, M. J., Newell, D. R., Yuen, K., Matthews, J. P., Balmano, K., Charlton, C. J., Gumbrell, L., Lind, M. J., Chapman, F., Proctor, M., Simmonds, D., Cantwell, B. M. J., and Calvert, A. H. Pharmacokinetics and pharmacodynamics of prolonged oral etoposide in women with metastatic breast cancer. *Cancer Chemother. Pharmacol.*, *37*: 161–167, 1995.
25. deJong, R. S., Mulder, N. H., Uges, D. R. A., Kaul, S., Winograd, B., Sleijfer, D. T., Groen, H. M. J., Willems, P. H. B., vanderGraaf, W. T. A., and deVries, E. G. E. Randomized comparison of etoposide pharmacokinetics after oral etoposide phosphate and oral etoposide. *Br. J. Cancer*, *75*: 1660–1666, 1997.
26. Harvey, V. J., Slevin, M. L., Joel, S. P., Smythe, M. M., Johnston, A., and Wrigley, P. F. M. Variable bioavailability following repeated oral doses of etoposide. *Eur. J. Cancer Clin. Oncol.*, *21*: 1315–1319, 1985.
27. Campbell, M. A., Perrier, D. G., Dorr, R. T., Alberts, D. A., and Finley, P. R. Methotrexate: bioavailability and pharmacokinetics. *Cancer Treat. Rep.*, *69*: 833–838, 1985.
28. Ogouey, D., Kolliker, F., Gerber, N. J., and Reichen, J. Effect of food on the bioavailability of low-dose methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum.*, *35*: 611–614, 1992.
29. Zimm, S., Collins, J. M., Riccardi, R., O'Neill, D., Narang, P. K., Chabner, B., and Poplack, D. G. Variable bioavailability of oral 6-mercaptopurine: is maintenance chemotherapy in acute lymphoblastic leukemia being optimally delivered? *N. Engl. J. Med.*, *308*: 1005–1009, 1983.
30. Juma, F. D., Rogers, H. J., and Trounce, J. R. Pharmacokinetics of cyclophosphamide and alkylating activity in man after intravenous and oral administration. *Br. J. Clin. Pharmacol.*, *8*: 209–217, 1979.
31. Struck, R. F., Alberts, D. S., Horne, K., Phillips, J. G., Peng, Y. M., and Roe, D. J. Plasma pharmacokinetics of cyclophosphamide and its cytotoxic metabolites after intravenous versus oral administration in a randomized cross-over trial. *Cancer Res.*, *47*: 2733–2726, 1987.
32. Hande, K. R. Etoposide pharmacology. *Semin. Oncol.*, *19* (Suppl.): 3–9, 1992.
33. Hande, K. R., Anthony, L., Hamilton, R., Sweetman, B., and Branch, R. Identification of etoposide glucuronide as a major metabolite of etoposide in the rat and rabbit. *Cancer Res.*, *48*: 1829–1834, 1988.
34. Relling, M. V., Nemecek, J., Schuetz, E. G., Schuetz, J. D., Gonzalez, F. J., and Korzekwa, K. R. O-demethylation of epipodophyllotoxins is catalyzed by human cytochrome P450 3A4. *Mol. Pharmacol.*, *45*: 352–358, 1994.
35. Leu, B. L., and Huang, J. D. Inhibition of intestinal p-glycoprotein and effects on etoposide absorption. *Cancer Chemother. Pharmacol.*, *35*: 432–436, 1995.

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