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Bioavailability of 50- and 75-mg oral etoposide in lung cancer patients

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Abstract This study was designed to determine the bioavailability of etoposide capsules administered orally at doses of 50 and 75 mg. Patients with inoperable or relapsed lung cancer, who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and adequate organ function, were eligible. A group of 17 patients were evaluable, all of whom were 75 years old or less, with an ECOG performance status of 0 or 1. The bioavailability of oral etoposide was determined by measuring the area under the etoposide plasma concentration versus time curve (AUC) on days 1, 10 and 21 during a once-daily regimen of oral administration for 21 consecutive days and comparing the value with the AUC achieved following intravenous administration 1 or 2 weeks after the last oral dose. The bioavailability of 50, 75 and 100 mg oral etoposide was determined in six, nine and two patients, respectively. The mean etoposide bioavailabilities ($\pm$ SD) of the 50-mg and 75-mg doses were 47 $\pm$ 11% and 59 $\pm$ 18%, respectively, and of the 100-mg dose in two patients were 51% and 33%, respectively. There was no statistically significant difference in bioavailability between the 50-mg and 75-mg doses. The bioavailability of low-dose oral etoposide was the same as that reported in previous higher dose oral etoposide bioavailability studies and that shown on the package insert supplied by the manufacturer. Improved bioavailability of low-dose oral etoposide was therefore not observed in a population of Japanese patients.

Key words Etoposide · Bioavailability

Introduction

Recent clinical trials have shown that long-term, low-dose oral etoposide administration is at least as effective as standard intravenous (IV) treatment regimens for the treatment of lung cancer [1–3]. Furthermore, the introduction of oral etoposide into combination chemotherapy regimens may shorten the hospitalization period and thus reduce treatment costs. Therefore, it may be reasonable to consider substituting oral for IV etoposide. In such circumstances we think it is vital to understand the detailed pharmacokinetic profile of the oral product in order to use the drug safely. As well as monitoring the AUC of an anticancer drug, knowing its bioavailability provides useful information when it is administered orally. Although several researchers have reported the bioavailability of oral etoposide used at higher doses [4–9] and Hande et al have reported the bioavailability of a 100-mg (two 50-mg capsules) dose of etoposide [10], there are, to our knowledge, no reports describing the precise bioavailability of both 50- and 75-mg doses, which are used most often in clinical practice. As we have explored the bioavailability profile of low-dose oral etoposide in our recent combination phase I study [11], we here present the bioavailability data for 50-, 75- and 100-mg oral doses of etoposide capsules.

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Patients and methods

Eligibility

Between July 1992 and July 1993, we conducted a combination phase I study of an IV carboplatin and chronic low-dose oral etoposide regimen [11]. Among 28 patients entered into this phase I study, 17 were evaluable for oral etoposide bioavailability. The eligible patients had histologically or cytologically confirmed lung cancer. Those with small-cell lung cancer were eligible if their disease was refractory or resistant to standard chemotherapy and radiotherapy regimens. All patients were required to be ≤ 75 years old and to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. Prior to starting the protocol, at least 4 weeks had to have elapsed since the last course of chemotherapy or radiotherapy, and in the case of a mitomycin C- and nitrosourea-containing regimen, at least 8 weeks had to have elapsed since the last course of chemotherapy. The patients were also required to have adequate bone marrow, hepatic and renal function, manifested as a white blood cell (WBC) count of $\geq 4000/\mu l$, a platelet count of $\geq 100{,}000/\mu l$, hemoglobin ≥ 10 g/dl, total serum bilirubin ≤ 1.5 mg/dl, serum transaminases $\leq 2 \times$ normal limit and serum creatinine ≤ 1.2 mg/dl. Patients with massive pleural effusion, ascites and/or pericardial effusion were considered ineligible, and those with another concomitant malignancy and/or other serious medical or psychiatric disease were also excluded. Patients with obvious evidence of disease progression during oral etoposide administration were removed from the study. All patients gave their informed consent prior to commencing the study.

Treatment plan

All the patients were in hospital during the study, and oral intake of etoposide was done under the supervision of a physician. Oral etoposide was given once daily for 21 consecutive days and carboplatin was administered IV over 1 h from 9:00 am within a dose range of 300–400 mg/m^2 on day 1. Etoposide capsules were taken with at least 150 ml water every morning (at 9:00 am) after breakfast. The content of breakfast was the same among all the patients. On the basis of the study by Harvey et al. [12], we thought it unnecessary for the patients to be fasted. For IV administration, etoposide was diluted to 500 ml with isotonic saline solution and administered over 1 h from 9:00 am without administration of prehydration or posthydration fluids. IV etoposide administration was given within 4 or 8 weeks after the start of oral etoposide administration and when 1 or 2 weeks had elapsed since the last oral etoposide administration. The IV doses of etoposide were 50, 75 and 100 mg for patients who took 50-mg, 75-mg and 100-mg capsules, respectively. IV etoposide was given as part of the treatment regimen for cancer, but on the day of IV administration no other anticancer drugs were administered.

Pharmacokinetic studies

Blood samples (5 ml) were drawn from each patient before, 30 min after, and 1, 2, 3, 4, 6, 8, 12 and 24 h after taking oral etoposide or after the start of etoposide infusion. When samples were taken on the day of IV carboplatin coadministration, 12-ml samples were drawn. Urine collection was done at 6-h intervals until 24 h after the start of treatment. The blood samples were centrifuged to remove the red blood cells, and both plasma and urine samples were stored at -80° C for a maximum of 2 weeks until the assays were carried out. The concentration of etoposide was measured using high-performance liquid chromatography (HPLC) [13], with a lower limit of detection of 100 ng/ml.

The AUCs were calculated using the trapezoidal method from zero to the last time-point measured, and from there to infinity by exponential extrapolation using the elimination rate constant. All the required pharmacokinetic parameters were calculated using the computer program MULTI [14].

The bioavailabilities of the 50- (one 50-mg capsule) and 75-mg (one 50-mg capsule and one 25-mg capsule) etoposide doses used were determined by comparing the AUC achieved following oral administration (AUC_{ORAL}) with that after an IV dose (AUC_{IV}):

$$\text{Bioavailability (\%)} = [(AUC_{ORAL})/(Dose_{ORAL})]/[(AUC_{IV})/(Dose_{IV})] \times 100.$$

The AUC_{ORAL} and AUC_{IV} values for each bioavailability calculation were obtained from the same individual patients.

Statistical analysis

The statistical analysis was performed using computer programs (StatView II, Avacus Concepts, Berkeley, Calif.) on a Macintosh PowerBook 170 microcomputer. Statistical comparisons were made using the two-tailed Student's t-test. Differences were considered statistically significant at $P < 0.05$.

Results

We were able to determine the bioavailability of etoposide capsules administered orally at doses of 50, 75 and 100 mg in six, nine and two patients, respectively. Of patients 1–17 (Figs. 1 and 2), numbers 3, 5, 8 and 16 were female, numbers 3, 5, 8, 9, 10 and 14 had previous treatment, the median age, was 58 years (range 42–73 years), and all were ECOG performance status ≤ 1.

The calculated $AUC_{0-\infty}$ values following a 50- or 100-mg IV and a 50- or 100-mg oral etoposide dose in each patient are shown in Fig. 1, and those following a 75-mg IV and 75-mg oral etoposide dose in each patient are shown in Fig. 2.

Table 1 shows the bioavailability based on the blood sampling day on which we obtained the oral etoposide AUC. The lowest row of data in Table 1 shows the mean ($\pm$ SD) bioavailability calculated from oral etoposide AUC data which we obtained on the nearest 1 or 2 weeks before the day of IV etoposide treatment, and IV etoposide AUC data obtained on the day of IV treatment (i.e. the oral AUC data for each patient on the far right of Figs. 1 and 2 were compared with the IV AUC data for each patient on the far left of Figs. 1 and 2). Only on day 1 was the bioavailability of the 75-mg dose higher than that of the 50-mg dose (unpaired Student's t-test, $P = 0.0481$), and on the other sampling day there was no difference in bioavailability between the 50- and 75-mg doses. The bioavailability of the 100-mg dose was 33% in one patient and 51.4% in the other.

The interpatient variability of bioavailability, reflected by the coefficient of variation at the 50-mg dose on days 1, 10 and 21 (first course), was 40%, 20% and 20%, respectively, and that at the 75-mg dose on days 1, 10 and 21 (first course) was 25%, 30% and 29%, respectively.

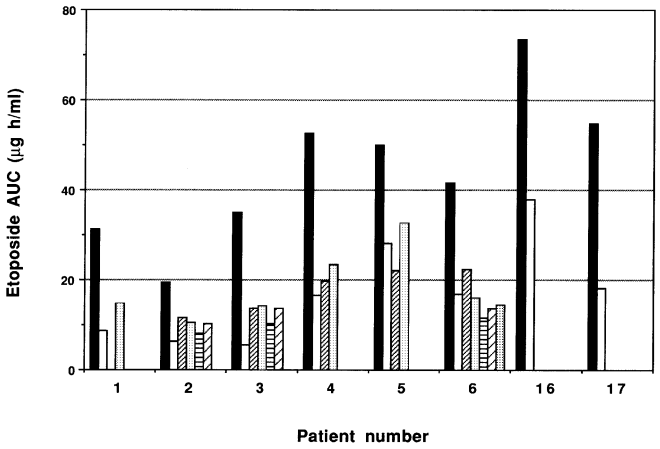

Fig. 1 AUCs (μg h/ml) measured following a 50-mg (patient numbers 1–6) and a 100-mg (patient numbers 16, 17) etoposide dose (■ IV administration, □ oral administration, first course day 1, ▨ oral administration, first course day 10, ▩ oral administration, first course day 21, ⊟ oral administration, second course day 1, ▨ oral administration, second course day 10, ▩ oral administration, second course day 21)

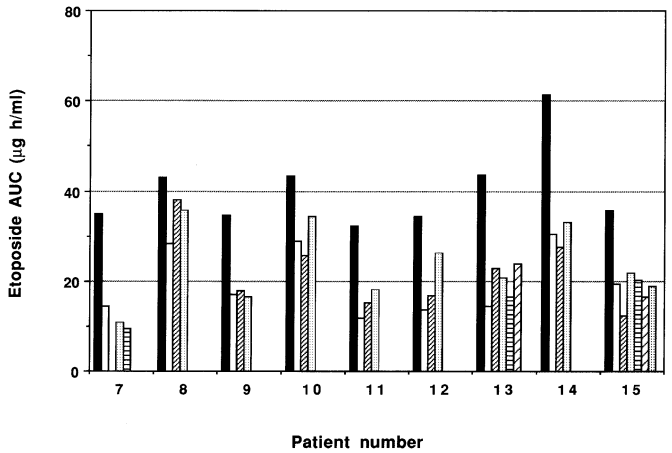

Fig. 2 AUCs (μg h/ml) measured following a 75-mg (patient numbers 7–15) etoposide dose (■IV administration, □ oral administration, first course day 1, ▨oral administration, first course day 10, ▩ oral administration, first course day 21, ⊟ oral administration, second course day 1, ▨ oral administration, second course day 10, ▩ oral administration, second course day 21)

In the same individuals, the bioavailability of the 50-mg dose on day 1 was significantly lower than that on days 10 and 21 (paired *t*-test, day 1 vs day 10, $P = 0.041$; day 1 vs day 21, $P = 0.01$), but there were no significant differences among the bioavailabilities on days 1, 10 and 21 when 75 mg was administered. The intrapatient variability, reflected by the coefficient of variation at the 50- and 75-mg doses, was 25% and 18%, respectively.

The pharmacokinetic parameters following IV doses are shown in Table 2. These values are slightly different from the previously reported values (elimination half-life, 4–8 h, volume of distribution (Vd), 7–17 l/m^2, plasma clearance, 15–35 ml/min per m^2, renal clearance, 6–10 ml/min per m^2, urine excretion, 20–45%) [15]. There were no statistically significant differences in the mean values for etoposide half-life, Vd, clearance, or urine excretion between IV doses of 50 mg and 75 mg (Table 2).

Table 1 Bioavailability of 50-mg and 75-mg oral doses of etoposide. Values are means ± SD

Time of sampling	Dose	
	50 mg	75 mg
1st course day 1	34.0 ± 13.6*	48.5 ± 12.0
1st course day 10	46.8 ± 9.5	53.5 ± 15.8
1st course day 21	48.2 ± 9.7	59.5 ± 17.2
Last day of oral intake	47.2 ± 10.7	59.0 ± 17.7

*$P = 0.0481$ vs 75-mg dose, first course day 1 (unpaired Student's *t*-test)

Table 2 Pharmacokinetic parameters following 50-mg and 75-mg IV etoposide doses. Values are means ± SD (*Vd* volume of distribution, CL_P plasma clearance, CL_R renal clearance)

Parameter	Dose	
	50 mg	75 mg
Elimination half-life (h)	5.4 ± 1.9	5.3 ± 1.1
Vd (l/m^2)	5.8 ± 0.6	6.4 ± 0.6
CL_P (ml/min/m^2)	16.5 ± 4.5	18.9 ± 2.9
CL_R (ml/min/m^2)	8.0 ± 3.8	7.7 ± 2.2
Urine excretion (%)	45.6 ± 11.5	39.4 ± 9.8

Discussion

In the present study we showed that the bioavailabilities of 50- and 75-mg oral etoposide doses were close to 50%. To date, few researchers have measured the actual bioavailability of low-dose (less than 100 mg) oral etoposide. Joel et al. reported a mean bioavailability of 59%, 64% and 48% on days 2, 14 and 15, respectively, for a 50-mg oral dose [16], and Cavalli et al. reported means (± SD) of 81 ± 24% with a 50-mg dose and 65 ± 21% with a 100-mg dose given orally [17], but both of these studies were published only in abstract form. The only carefully designed and fully described clinical evaluation of low-dose oral etoposide bioavailability is that reported by Hande et al [10]. In a review of previous reports and the results of their own study, Hande et al. drew attention to the high bioavailability of a 100-mg oral dose (two 50-mg capsules); their mean (± SD) was 76 ± 22%. However, our present results are not in accordance with theirs.

Our study may have had several drawbacks: oral etoposide was given after breakfast; the data were

based partly on the oral etoposide AUCs obtained on day 1 when carboplatin was coadministered and oral etoposide was given for 21 consecutive days. The effect of food was considered to be negligible because patients took the same breakfast, and a previous report has described no effect of food on etoposide bioavailability [12]. We observed that oral etoposide bioavailability was close to 50% excluding the bioavailability data based on day 1, and we considered that prolonged administration neither induced etoposide accumulation nor had any effect on etoposide pharmacokinetics, since oral etoposide AUCs and other pharmacokinetic parameters on days 10 and 21 were the same [11] (Figs. 1 and 2).

As pointed out by Hande et al., the contents of the capsules available commercially in Europe differ slightly from those of the preparations marketed in the United States. However, the capsules available in Japan are identical to those from the United States (Bristol Myers Squibb, KK, and Nippon Kayaku). In addition, we measured the AUC from zero to infinity. Therefore, the reported variability of low-dose oral etoposide bioavailability is most likely due to interpatient variability based on ethnic differences in oral etoposide metabolism or some other unknown mechanism.

Inherited differences in liver cytochrome P-450 are one of the best known examples of pharmacogenetic variability. Recently, P-450 IIIA4 (CYP3A4) was reported to be the predominant human P-450 responsible for *O*-demethylation of etoposide to its catechol metabolite [18], and another report suggests that increased CYP3A4 induced by anticonvulsant therapy may be associated with increased plasma clearance of teniposide, a structurally similar epipodophyllotoxin, [19]. Comparing the mean ($\pm$ SD) AUCs of IV etoposide between our study (50-mg dose, 38.4 ± 12.4 μg h/ml, 75-mg dose, 40.3 ± 9.0 μg h/ml) and that of Hande et al. (100-mg dose, 39.1 ± 10.0 μg h/ml), we can speculate that the AUC for Japanese is higher than that for Caucasians for the same dose. In addition, comparing the plasma clearance of IV etoposide between our study (Table 2) and others [10, 15], the clearance in Japanese seems to be lower. Also, the fact that patients in the present study did not receive any drugs known to modulate P-450 activity suggests a lower degree of liver metabolism mediated by P-450s in the Japanese population and the existence of an ethnic difference in etoposide metabolism.

On the other hand, a decreased AUC following oral administration in the Japanese population can be argued. As our oral etoposide phamacokinetic parameters on day 1 were probably influenced by carboplatin coadministration [11], we discuss here the data of day 10 and day 21. Comparing the mean ($\pm$ SD) AUC of the 50-mg dose of oral etoposide between our study ($n = 15$, 16.9 ± 6.0 μg h/ml; range 10.3–32.5 μg h/ml) and that of Cavalli et al. (range 17.5–31.6 μg h/ml), the AUC for Japanese would be lower than that for Caucasians. However, other pharmacokinetic values of the 50-mg dose in our study (elimination half life, 6.4 ± 2.7 h, apparent oral clearance 37.2 ± 8.5 ml/min per m^2, renal clearance, 8.2 ± 2.5 ml/min per m^2, urine excretion, 20.6 ± 5.7%) cannot be compared with those for Caucasians since there are no precise pharmacokinetic data for 50-mg and 75-mg oral etoposide except ours.

Recently, several researchers have reported the presence of CYP3A4 protein and its activity in the human intestinal wall in addition to the liver [20, 21]. If the intraenterocytic metabolism of etoposide were higher in the Japanese population than in Caucasians and etoposide metabolism in the intestinal wall is crucial, the increased first-pass metabolism in the intestine might explain the lower bioavailability in this study in comparison with others [10, 17]. Indeed, orally administered cyclosporin is reported to be substantially metabolized by P-450 IIIA in the small intestine, which explains its low bioavailability [22, 23].

In any event, whether or not modulation of CYP3A4 activity or oral etoposide metabolism by other drugs has a significant impact in clinical practice remains to be elucidated.

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