Eur J Cancer Clin Oncol, Vol. 21, No. 11, pp. 1315–1319, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Variable Bioavailability Following Repeated Oral Doses of Etoposide

V. J. HARVEY,* M. L. SLEVIN,*† S. P. JOEL,* M. M. SMYTHE,‡ A. JOHNSTON‡ and P. F. M. WRIGLEY*

Imperial Cancer Research Fund Department of Medical Oncology, St Bartholomew's and Hackney Hospitals, London and ‡Department of Clinical Pharmacology, St Bartholomew's Hospital, London, U.K.

Abstract—*Following oral administration considerable variation in the bioavailability of etoposide has been reported between patients and with different formulations of the drug. The variation within patients following repeated doses is unknown and has therefore been studied in seven patients receiving therapy on three successive days for relapsed small cell lung carcinoma. Etoposide was administered at a dose of* 400 mg *orally and plasma concentrations were measured using high-performance liquid chromatography. Within-patient coefficients of variation over three successive days ranged over* 19–45% *for peak plasma concentrations and* 16–53% *for the area under the plasma concentration–time curve. There was no evidence of a trend to suggest improving or worsening absorption and accumulation did not occur. Urinary excretion was* < 25% *and showed no increase over the* 3 days. *These data indicate that etoposide bioavailability is not constant and oral therapy may lead to unsuspected underdosing or unexpected toxicity in schedules extending over several days. Monitoring blood concentrations for a single day following oral therapy may give a misleading idea of the total bioavailability of etoposide during a course of therapy. Studies of the relationship between the pharmacokinetics of prolonged schedules of etoposide and disease outcome may lead to unreliable conclusions unless intravenous etoposide is used.*

INTRODUCTION

ETOPOSIDE is a cytotoxic agent derived from podophyllotoxin [1], which is established in the treatment of several malignancies [2–19], including small cell lung carcinoma, germ cell lung tumours and lymphomas. It has been shown to exhibit schedule dependency in experimental systems [10, 11] and possibly also in man [12]. As a consequence it is usually given over several days [2, 3, 13, 14]. In common with much chemotherapy it is frequently given as part of a combination regimen [4], particularly in those tumours in which it shows greatest activity [5–7, 9, 15].

The majority of studies of etoposide pharmacokinetics have followed single doses of the drug and have shown marked variation between patients following both intravenous [16–19] and oral [16, 17, 20–22] administration. Despite the frequent administration of etoposide over several days, there are few data on the pharmacokinetics of repeated doses and none for repeated oral administration. D'Incalci and co-workers have shown virtually identical plasma concentrations after the first and fifth intravenous doses of a 5-day course, with no evidence of accumulation in two patients [17]. The absence of data concerning within-patient variation following oral administration prompted the study reported here.

MATERIALS AND METHODS

Patients

Seven adult patients receiving treatment either for relapsed extensive small cell lung carcinoma (five patients) or for previously untreated diffuse malignant mesothelioma (two patients) were studied. All were ambulant (Karnofsky score > 60% [23]) and all had normal bone marrow, renal and hepatic function. There was no clinical evidence of gastrointestinal disturbance.

Accepted 23 May 1985.

†To whom correspondence and requests for reprints should be addressed at: Department of Medical Oncology, St Bartholomew's Hospital, London EC1A 7BE, U.K.

Treatment

Therapy consisted of etoposide capsules, 400 mg, as a single dose on each of three successive days. The capsules were administered after an overnight fast with the patient sitting in bed and with sufficient water (approximately 100–200 ml) to allow swallowing. The five patients with extensive small cell lung carcinoma received etoposide as part of a combination regimen but the other drugs (adriamycin and procarbazine) were administered on day 4 after the completion of the pharmacokinetic study. The two patients with diffuse malignant mesothelioma received etoposide as a single agent administered over 5 days, but underwent pharmacological study only on the first 3 days. Antiemetic therapy was not required and no patients vomited.

Sampling and assay

After an overnight fast an heparinised polyethylene catheter was introduced into a suitable forearm vein under local anaesthesia. A pretreatment sample was taken. After etoposide administration blood samples were taken at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12 and 24 hr. Blood samples were taken into lithium heparin tubes, centrifuged, separated and the plasma stored at -20°C until assay. Urine was collected from the time of etoposide administration for 24 hr. The total quantity for each day was measured and an aliquot taken and stored at -20°C until assay.

Assay was performed using reverse-phase high-performance liquid chromatography with detection by ultraviolet absorbance at 229 nm as previously described [24]. The lower limit of sensitivity was <100 ng/ml and coefficients of variation were <4% within-run and <7% between-run.

Calculation and statistics

Pharmacokinetic profiles were plotted using STRIPE [25], an interactive computer program, for the analysis of drug pharmacokinetics. This program calculates the area under the plasma concentration-time curve (AUC) by the trapezoidal method and extrapolates to infinity. The effect of the residual concentrations from the previous day, where appropriate (i.e. days 2 and 3), were removed by curve stripping. AUC values are presented corrected to a standard surface area of 1.7 m^2 to compensate for the fixed dosage to patients of varying body size. The volume of distribution (V_d) was calculated from the formula

$$V_d = \frac{\text{dose}}{\text{AUC} \times k},$$

where k = elimination rate constant. Clearance (Cl) was obtained from the formula

$$Cl = \frac{V_d \times k}{60},$$

and bioavailability from the ratio AUC_{oral}: $AUC_{intravenous}$, expressed as a percentage.

Statistical significance was calculated using Student's t test.

RESULTS

The pharmacokinetic data for the 3 days are shown in Table 1. Mean results for elimination half-life, peak plasma concentration, AUC and percentage of dose excreted in the urine in 24 hr were not significantly different for the 3 days.

There was, however, marked variation within patients over the 3 days, particularly in peak plasma concentrations (>2-fold variation in 4/7 patients) and in AUC (>2-fold variation in 2/7 patients and >1.5-fold variation in a further four patients). Mean results for the individual patients together with the coefficients of variation are shown in Table 2 and represented diagrammatically in Fig. 1 (peak plasma concentration) and Fig. 2 (AUC). Despite the variation within patients, there was no trend to accumulation or decreasing concentrations over the 3 days.

Urinary excretion also varied considerably, but was universally <25% and did not increase over the 3 days.

Table 1. Pharmacokinetics of oral etoposide (400 mg) *following repeated administration over 3* days (*mean results* ± 95% *confidence limits*)

	Day 1	Day 2	Day 3
Elimination half-life (hr)	6.7 ± 1.5	7.3 ± 2.6	6.8 ± 1.4
Peak plasma conc. (μg/ml)	14.2 ± 6.0	12.1 ± 4.9	16.5 ± 10.5
AUC (μg/ml.hr/min/1.7 m^2)	93.2 ± 31.5	88.2 ± 26.5	109.1 ± 50.1
Urinary excretion (% of dose given)	12 ± 6	12 ± 3	15 ± 6

*Table 2. Within-patient variation in pharmacokinetic data following oral etoposide on three successive days**

Patient	Peak plasma concentration (μg/ml)	CV† (%)	AUC (μg/ml.hr)	CV (%)
1	16.4	27.5	105.2	24.2
2	10.4	44.1	97.8	22.5
3	8.7	45.4	43.0	45.7
4	25.8	42.3	136.1	52.7
5	17.2	22.8	109.4	15.8
6	7.1	19.1	83.3	23.9
7	11.4	42.7	103.0	28.6

*Mean data over 3 days.
†Coefficient of variation.

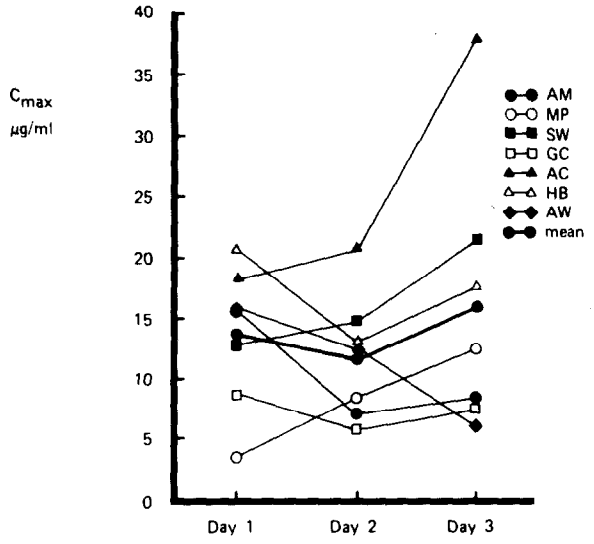

Fig. 1. Peak plasma concentrations of etoposide in individual patients following oral administration on three successive days.

DISCUSSION

These data show substantial within-patient variation over three consecutive days without any evidence of accumulation or decrease in the bioavailability of etoposide over this time. The explanation for this variation is not easily apparent.

Many of the usual reasons for variable bioavailability were eliminated in this study. Patients acted as their own control. Therapy was administered over only three consecutive days, given consistently after an overnight fast, with the patient assuming the same sitting posture with sufficient water for complete swallowing [26], without concomitant therapy and with only one formulation of the drug. Etoposide is poorly soluble in water [2], but in the formulation used was already dissolved in a mixture of organic solvents, thus removing the problem of drug dissolution, the most common rate-limiting step in drug absorption [27]. Although there was no

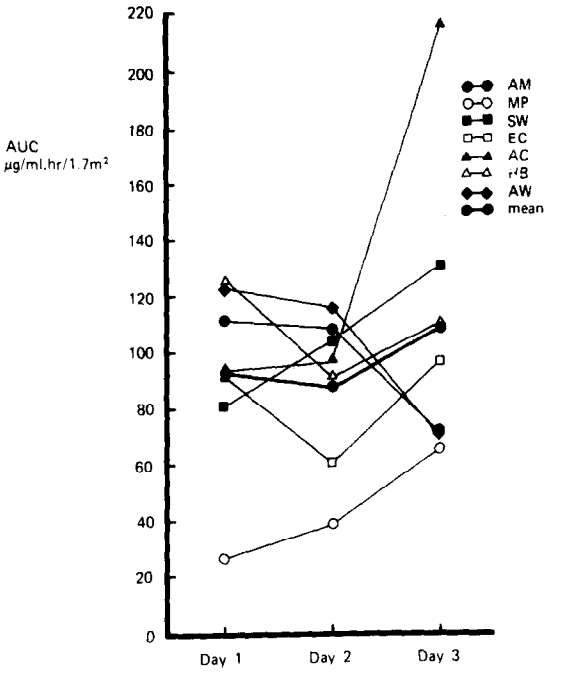

Fig. 2. AUC in individual patients following oral etoposide administration on three successive days.

obvious gastrointestinal toxicity and no patient vomited, a few patients felt mildly nauseated and this may have affected the rate of gastric emptying. On the other hand, there was little variation within patients in the time to peak plasma concentrations, which was achieved in all patients between 45 min and 2 hr. The most obvious variable was the preceding doses of etoposide in patients treated on days 2 and 3. While this might explain consistent improvement or worsening of absorption, it is difficult to understand how this explains the inconsistent pattern noted.

It has been suggested that the bioavailability of oral etoposide may be non-linear above 200 mg [21] and therefore the dose of 400 mg used in this study may have accentuated any variability in absorption. Such an explanation suggests the need for further studies of within-patient variation at lower doses.

The observation reported here raises questions with regard to the reliability of bioavailability in therapeutic schedules of 3-5 days duration. Erratic bioavailability as shown here cannot be taken into account and it is possible that successive courses may lead to over- or under-dosing. The variation within patients may result in other difficulties. Attempts to relate the pharmacokinetics of oral etoposide to tumour response or to study the effect of schedule on outcome will require the drug concentrations in the plasma to be monitored for the entire course as those present on a single day may give a misleading estimation of the total bioavailability.

Alternatively, intravenous therapy should be used in these studies.

While the oral route of administration remains a useful, practical and convenient means of giving etoposide, the data have suggested that absorption may be erratic. Such variation may be difficult to recognise during schedules of therapy extending over several days and in the presence of other chemotherapy.

REFERENCES

1. Horwitz SB, Loike JD. A comparison of the mechanism of action of VP-16-213 and podophyllotoxin. *Lloydia* 1977, **40**, 82-89.
2. Arnold AM. Podophyllotoxin derivative VP-16-213. *Cancer Chemother Pharmacol* 1979, **3**, 71-80.
3. Nissen NI, Dombernowsky P, Hansen HH, Pedersen AG. The epipodophyllotoxin derivatives VM-26 and VP-16-213, 1976-1979, a review. *Recent Results Cancer Res* 1980, **74**, 98-106.
4. Issell BF, Crooke ST. Etoposide (VP-16-213). *Cancer Treat Rev* 1979, **6**, 107-124.
5. Williams SD, Einhorn LH. Etoposide salvage therapy for refractory germ cell tumors: an update. *Cancer Treat Rev* 1982, **9** (Suppl. A), 67-71.
6. Goldhirsch A, Joss R, Cavalli F, Brunner KW. Etoposide as single agent and in combination chemotherapy of bronchogenic carcinoma. *Cancer Treat Rev* 1982, **9** (Suppl. A), 85-90.
7. Itri LM, Gralla RJ. A review of etoposide in patients with non-small-cell lung cancer (NSCLC). *Cancer Treat Rev* 1982, **9** (Suppl. A), 115-118.
8. Kroner T, Obrecht JP, Jungi WF for the Swiss Working for Clinical Cancer Research (SAKK). Etoposide as single agent and in combination with *cis*-platinum for malignant lymphomas. *Cancer Treat Rev* 1982, **9** (Suppl. A), 39-43.
9. Rivera G, Bowman WP, Look AT, Evans WE, Kalwinsky D, Dahl G. Single-agent and combination chemotherapy with etoposide in the acute leukemias of childhood. *Cancer Treat Rev* 1982, **9** (Suppl. A), 53-57.
10. Dombernowsky P, Nissen NI. Schedule dependency of the antileukemic activity of the podophyllotoxin-derivative VP 16-213 (NSC-141540) in L1210 leukemia. *Acta Path Microbiol Scand (Sect A)* 1973, **81**, 715-724.
11. Rozencweig M, von Hoff DD, Henney JE, Muggia FM. VM26 and VP16-213, a comparative analysis. *Cancer* 1977, **40**, 334-342.
12. Cavalli F, Sonntag RW, Jungi F, Senn HJ, Brunner KW. VP-16-213 monotherapy for remission induction of small cell lung cancer: a randomised trial using three dosage schedules. *Cancer Treat Rep* 1978, **62**, 473-475.
13. Issell BF. The podophyllotoxin derivatives VP16-213 and VM26. *Cancer Chemother Pharmacol* 1982, **7**, 73-80.
14. Radice PA, Bunn PA Jr, Ihde DC. Therapeutic trials with VP-16-213 and VM-26: active agents in small cell lung cancer, non-Hodgkin's lymphomas and other malignancies. *Cancer Treat Rep* 1979, **63**, 1231-1239.
15. Comis RL. Small cell carcinoma of the lung. *Cancer Treat Rev* 1982, **9**, 237-258.
16. Harvey VJ, Slevin ML, Joel SP *et al.* The pharmacokinetics of VP16 (etoposide) and bioavilability following different methods of administration (abstract). *Br J Clin Pharmacol* 1984, **17**, 204-205.
17. D'Incalci M, Farina P, Sessa C *et al.* Pharmacokinetics of VP16-213 given by different administration methods. *Cancer Chemother Pharmacol* 1982, **7**, 141-145.
18. Creaven PJ, Allen LM. EPEG, a new antineoplastic epipodophyllotoxin. *Clin Pharmacol Ther* 1975, **18**, 221-226.
19. Allen LM, Craven PJ. Comparison of the human pharmacokinetics of VM-26 and VP-16, two antineoplastic epipodophyllotoxin glucopyranoside derivatives. *Eur J Cancer* 1975, **11**, 697-707.
20. Harvey VJ, Slevin ML, Joel SP, Johnston A, Wrigley PFM. The effect of food and concurrent oral chemotherapy on the absorption of etoposide (abstract). *Br J Clin Pharmacol* 1984, **17**, 639-640.
21. Harvey VJ, Slevin ML, Joel SP, Johnston A, Wrigley PFM. The effect of dose on the absorption of oral etoposide (abstract). *Br J Cancer* 1984, **49**, 387.
22. Beveridge T, Kalberer F, Neusch E. Bioavailability study with ^{3}H-VP 16-213 in man. Internal report (Sandoz Ltd) Basle, 1976.
23. Karnofsky DA, Abelman WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma: with particular reference to broncheogenic carcinoma. *Cancer* 1984, **1**, 634-656.

24. Harvey VJ, Joel SP, Johnston A, Slevin ML. High performance liquid chromatography of etoposide in plasma and urine. *J Chromatogr* 1985, **339**, 419-423.
25. Johnston A, Woollard RC. STRIPE: an interactive computer program for the analysis of drug pharmacokinetics. *J Pharmacol Methods* 1983, **9**, 193-200.
26. Channer KS, Virjee J. Effect of posture and drink volume on the swallowing of capsules. *Br Med J* 1982, **285**, 1702.
27. Wade DN. The therapeutic performance of drug products. In: Avery GS, ed. *Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics*, 2nd Edn. Sydney, Addis Press, 1980, 182-201.