Cancer Chemother Pharmacol (1989) 24: 329–331

Cancer Chemotherapy and Pharmacology

The effect of dose on the bioavailability of oral etoposide: confirmation of a clinically relevant observation*

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Summary. The effect of dose on the bioavailability of oral etoposide was investigated in ten patients with malignant mesothelioma who received single-agent etoposide as part of a phase II study. Etoposide pharmacokinetics were studied in each patient at oral dose levels of 100, 200, 300, 400 and 600 mg. At doses above 200 mg, the AUC and peak concentrations of etoposide were substantially lower than predictions based on the 100-mg dose. This study confirms previous observations that etoposide absorption is dose-dependent and that a mean bioavailability of approximately 50% cannot be assumed at total oral doses >200 mg.

Introduction

Etoposide is a cytotoxic drug with a wide spectrum of activity in a range of haematological and solid malignancies [2, 12, 15, 20]. Date from animal studies [16, 19] as well as in man [4, 18] demonstrate considerable schedule dependency requiring the drug to be given over several days. This makes the oral formulation an attractive proposition, as i.v. administration is both inconvenient and potentially expensive for patients, often requiring admission to hospital for several days per cycle.

The bioavailability of oral etoposide is approximately 50%, and is very variable both within and between patients [3, 6, 8, 17]. A previous study from this institution has suggested that etoposide bioavailability may decrease with increasing dose [10]. This observation may have potential importance when calculating the oral dose of etoposide on the basis of the Phase I and II studies, which, to date, have used predominantly intravenous etoposide. The information is also critical in determining whether the recently developed high-dose etoposide schedules [5, 21, 22] can be given orally. The present study was conducted to confirm the above-mentioned initial observation [10] and expand the dose range studied over a larger number of patients.

Materials and methods

Patients. Ten patients receiving single-agent etoposide as part of a phase II study in histologically confirmed malignant mesothelioma were investigated. Patients were aged 70 years or less, with a Karnofsky performance status [14] of >60% and adequate liver and renal function. Minor rises in liver enzymes related to disease involvement of the liver did not exclude patients from the study. Gastrointestinal function was clinically normal.

Treatment. Each patient received five separate oral doses of etoposide at 100, 200, 300, 400 and 600 mg over 5 consecutive days. The order in which the doses were given was randomised to exclude an order affect. The drug was given after an overnight fast, and food and drink were allowed 2 h after treatment. A pre-treatment blood sample was taken from a forearm vein by a polythene catheter and further samples were taken at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10.0, 12.0 and 24.0 h after treatment. Samples were drawn into lithium heparin and after centrifugation the separated plasma was stored at −20°C until analysis. A 24-h urine sample was collected over each treatment period and an aliquot stored at −20°C until analysis.

Assay. Analysis of etoposide was carried out by a previously described method [9] using chloroform extraction with di-phenylhydantoin as an internal standard. Quantitative determination is then done by HPLC, with UV detection at 229 nm, which gives a lower sensitivity limit of <100 ng/ml and reproducibility of <4% within and <7% between runs.

Pharmacokinetic calculation. Calculation of pharmacokinetic parameters was achieved using STRIPE [13], an interactive computer programme for the analysis of drug pharmacokinetics. The AUC was calculated by the trapezoidal method extrapolated to infinity using the elimination-rate constant. On days 2–5, residual drug concentrations from the previous dose were stripped prior to pharmacokinetic analysis using the formula

$$Cp = Cp^0 \cdot e^{kel \cdot t},$$

where Cp represents the drug concentration at time t, Cp^0 the drug concentration at time 0 and k_{el} the elimination rate constant.

Results

The mean pharmacokinetic data for the patients is given in Table 1. The AUC at each dose and the predicted AUC calculated from the 100-mg dose are shown in Fig. 1. The peak concentration at each dose and the predicted peak

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Table 1. Mean pharmacokinetic data (*t*-SD) for ten patients following oral etoposide

	100 mg	200 mg	300 mg	400 mg	600 mg
Elimination half-life (h)	8.08± 1.48	8.05± 4.12	8.34± 3.18	8.16± 1.95	6.95± 1.96
Measured peak concentration (μg/ml)	4.70± 2.05	8.40± 3.32	10.02± 5.00	12.02± 4.82	16.40± 7.31
AUC (μg/ml · h/1.7 m²)	38.8 ± 8.3	68.9 ±29.6	93.5 ±38.1	105.3 ±41.3	139.5 ±44.8
Urinary excretion (% of dose)	34 ±25	26 ± 7	19 ± 9	15 ± 8	13 ± 7
Student's *t*-test (*P* value) AUC/100 mg vs AUC at 100 mg	–	0.3	0.061	<0.001	<0.001

Table 2. Percentage increase in AUC over 100 mg at higher oral doses of etoposide in ten patients

Patient	200 mg (%)	300 mg (%)	400 mg (%)	600 mg (%)
1	49	117	95	166
2	177	208	309	184
3	107	56	98	262
4	46	197	174	413
5	–20	20	156	267
6	68	99	128	326
7	77	74	183	309
8	143	284	265	165
9	3	98	79	121
10	152	291	242	410
Mean	84	145	173	262
SD	59	95	78	103
Predicted increase over 100 mg	100	200	300	500

concentration calculated from the 100-mg dose are shown in Fig. 2. Mean plasma concentration-time curves at each dose are shown in Fig. 3. Also shown in Table 1 are the results of a Student's *t*-test of AUC/100 mg at the higher doses vs the AUC at 100 mg. The difference between the AUC/100 mg VS AUC at 100 mg almost achieved statistical significance at the 300-mg dose and were highly significant at the 400- and 600-mg doses. Table 2 shows the actual percentage increase in AUC at each dose for individual patients, compared with their own 100-mg AUC values.

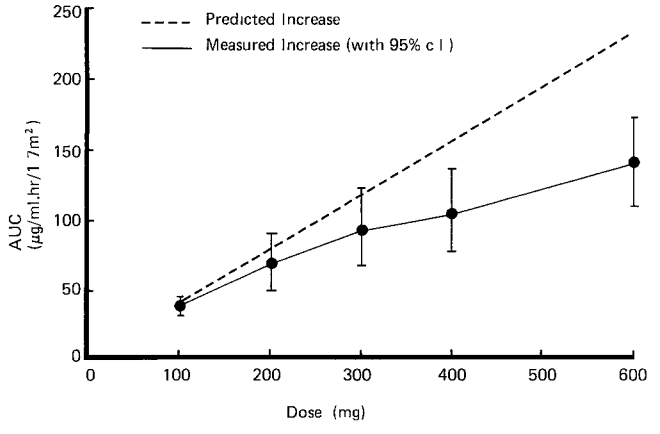

Fig. 1. Mean AUC in ten patients at increasing doses of etoposide

Multiple linear regression analyses of AUC vs dose and day number (days 1–5) gave an *r* value of 0.63 for dose ($F = 31.8$) and −0.005 for day ($F = 0.00$), showing no relationship between the day of administration within the 5-day course and AUC.

Discussion

The data reported demonstrate that the AUC achieved after oral etoposide fails to reach predicted levels at doses as low as 300 mg. This decrease in AUC relative to a 100-mg dose becomes highly significant at doses above 300 mg. Furthermore, this trend is reflected in the peak concentrations, as shown in Fig. 2, and the dose excreted in the urine, as shown in Table 1. These findings are in agreement with the results of the previous study [10], although the relative decrease in absorption at doses above 400 mg was more gradual than that found previously.

Multiple linear regression analyses show that the only significant factor in predicting the AUC was the drug dose ($F = 31.8$) and that the day of administration was not significant ($F = 0.00$). This would indicate that the drug was not exerting any effect on its own uptake from the gut, thereby impairing absorption on subsequent days. The pharmacokinetic data derived from this study do not readily suggest an explanation for the decrease in bioavailability of etoposide with increasing dose. If this were due to the saturation of the transport system in the gut, a plateau in the concentration-time curve would be expected as the process reaches the maximal rate. Such a plateau was not found at the higher doses.

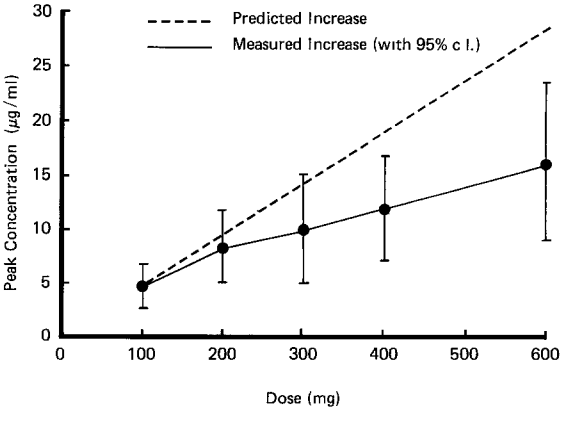

Fig. 2. Mean peak plasma concentration of etoposide in ten patients

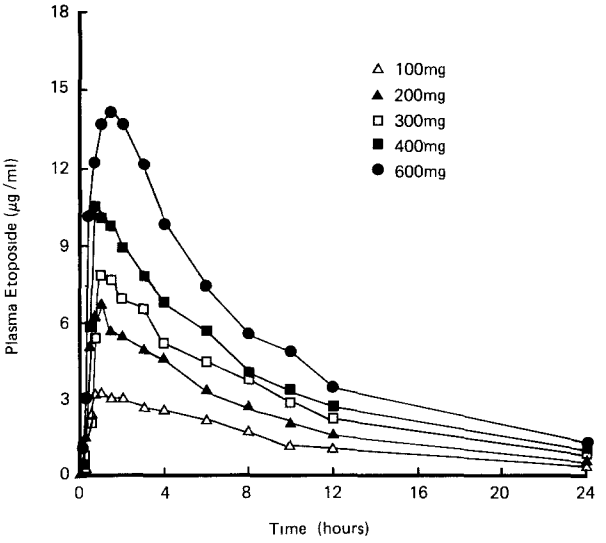

Fig. 3. Mean plasma concentration time curves in ten patients

Etoposide is 96% protein-bound [1], and the saturation of this binding with a concomitant increase in free or unbound etoposide may theoretically lead to an apparent decrease in bioavailability at higher doses, due to more rapid clearance of the free fraction after absorption. However, urinary excretion data, as shown in Table 1, demonstrate that the proportion of the dose excreted in the urine decreases with increasing dose. Furthermore, pharmacokinetic studies of i.v. etoposide have not shown dose-dependent pharmacokinetics [7, 11].

This study confirms that the oral bioavailability of etoposide decreases with increasing dose and demonstrates that a mean oral bioavailability of 50% can only be assumed at a total oral dose of <300 mg. In clinical practice, these findings need not influence the use of oral etoposide where the main intent of treatment is palliative (although doses should be limited to <400 mg). However, for cases where etoposide is used with curative intent, this study confirms that the oral route is too unreliable in terms of both day-to-day variability and dose-related bioavailability to ensure adequate drug delivery to the tumour; in these cases, parenteral administration should always be used.

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Received March 10, 1988/Accepted August 5, 1988