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Pharmacological attempts to improve the bioavailability of oral etoposide

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Abstract Etoposide demonstrates incomplete and variable bioavailability after oral dosing, which may be due to its concentration and pH-dependent stability in artificial gastric and intestinal fluids. The use of agents that may influence etoposide stability and, thereby, bioavailability, was investigated in a number of clinical studies. Drugs that influence the rate of gastric emptying, while modulating the time of drug absorption, did not significantly alter the etoposide area under the concentration-time curve (AUC) or bioavailability. Specifically, metoclopramide had little effect on the etoposide absorption profile and did not significantly alter the AUC (AUC with etoposide alone, 68.4 ± 20.3 μg ml^{-1} h, versus 74.3 ± 25.9 μg ml^{-1} h with metoclopramide), suggesting that in most patients the drug is already emptied rapidly from the stomach. In contrast, propantheline produced a dramatic effect on etoposide absorption, delaying the time of maximal concentration t_{max} from 1.1 to 3.5 h ($P < 0.01$), but again without a significant improvement in drug AUC or bioavailability across the 24-h study period (AUC with etoposide alone 78.3 ± 19.1 μg ml^{-1} h, versus 88.1 ± 23.6 μg ml^{-1} h with propantheline). The effect of these drugs on the absorption of oral paracetamol, a drug included in the study as a marker of gastric emptying, was exactly the same as that found for etoposide, with no change in AUC being observed after metoclopramide or propantheline administration but a significant delay in t_{max} being seen on co-administration with etoposide and propantheline. The co-administration of ethanol or bile salts (agents that significantly improved the stability of etoposide in artificial intestinal fluid) with oral etoposide similarly had no effect on improving the etoposide AUC or reducing the variability in AUC, suggesting that drug stability in vivo was not affected by these agents. In the third study the co-administration of cimetidine had no effect on the pharmacokinetics of oral or i.v. etoposide, despite the previous observation that etoposide stability was markedly improved at pH 3–5 as compared with pH 1 in artificial gastric fluid. This series of studies, designed to investigate factors that improved etoposide stability in laboratory studies, failed to demonstrate any potentially useful improvement in AUC or bioavailability in the clinical setting.

Key words Etoposide · stability · pharmacokinetics bioavailability

Introduction

Etoposide, a semi-synthetic podophyllotoxin, is active in a number of malignancies and is perhaps the most active single agent in the treatment of small-cell lung cancer [35, 55]. It has been clearly demonstrated to have greater efficacy in humans when used with more prolonged schedules of administration [55], for which oral etoposide is the most convenient dosing form. However, the oral bioavailability of etoposide is only approximately 50% [22], with considerable variability being observed both within and between patients [25, 57] and with decreasing bioavailability occurring with increasing dose [54], factors that result in unreliable dosing with oral administration. Although a recent report suggested that the bioavailability of etoposide at lower oral doses [100 mg] may be as high as 76%, there was nonetheless still significant inter-patient variability, with the coefficient of variation being 29%, and the range, 34–100% [20]. Evidence gathered to

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date suggests that etoposide bioavailability is not significantly affected by food [26].

In vitro studies have shown that the stability of etoposide is reduced in intestinal fluid as compared with gastric fluid and that this loss of stability is dependent on both time and concentration [33]. The stability of etoposide is also improved in artificial gastric fluid at pH 3 and pH 5 over pH 1, and in artificial intestinal fluid it was greatly improved by the addition of ethanol or bile salts. These observations and previous reports [53], suggest that the poor and variable oral bioavailability of etoposide may be related to its poor stability in physiological fluids. This paper describes several pharmacological approaches aimed at improving the stability and, thereby, the bioavailability of oral etoposide, involving the modification of gastric emptying time and stomach pH and the co-administration of etoposide with agents that improved etoposide stability in the in vitro studies [33].

Gastric emptying time accounts for much of the individual variation in the absorption of a drug [49]. With etoposide this factor may take on even more significance as its stability in intestinal fluid is concentration-dependent, which results in even greater variability in drug absorption [33]. The amount and, therefore, concentration, of etoposide in the upper small bowel will be influenced by the rate of gastric emptying, and modification of gastric emptying may thus alter etoposide concentration in intestinal fluid and improve drug stability and bioavailability. The first study described in this paper was conducted to assess prospectively whether the pharmacokinetics of oral etoposide are affected by metoclopramide or propantheline, both of which alter gut transit times. Metoclopramide reduces small bowel transit time [21] and, although it has been shown to speed gastric emptying in normal volunteers [2, 14], this effect has been most readily demonstrated in other studies in patients with slow rates of gastric emptying [8, 18, 32, 46]. Propantheline slows both gastric emptying time [14, 29, 30, 46] and small intestinal transit [12]. To determine gastric emptying time in the studies reported in this paper, patients were also given paracetamol, a compound that is not absorbed from the stomach and has been shown to correlate well with the more formal radioisotopic techniques for determining gastric emptying time [7, 27, 47].

The in vitro studies of oral etoposide stability describe that the addition of either ethanol or the bile salt sodium tauroglycocholate improve the stability of etoposide in artificial intestinal fluid [33]. These agents may therefore be useful clinically in that they may improve the absorption of etoposide by keeping the drug in solution to a greater degree and for a longer duration. In the second study described herein the pharmacokinetics of oral etoposide were compared in patients with and without the co-administration of ethanol and sodium tauroglycocholate.

Cimetidine is an H2 receptor antagonist that competitively inhibits the interaction of histamine with H2 receptors, thereby inhibiting gastric acid secretion and reducing stomach acidity. As the stability of etoposide in gastric fluid was improved at pH 3 and 5 over pH 1 [33], the administration of oral etoposide to patients receiving cimetidine may result in improved gastric stability and, thereby, improved bioavailability. In addition to this interaction, the pharmacokinetics of etoposide could be altered by cimetidine's inhibitory action on the cytochrome P450 enzyme system [10, 48], hepatic enzymes involved in oxidative metabolism. This has been reported to result in elevated blood levels of a number of drugs in patients receiving cimetidine [56], including warfarin [52], diazepam [38], theophylline [44], phenytoin [45], propranolol [51], and procainamide [3]. The metabolism of etoposide is poorly understood, and the possibility of an interaction involving the inhibition of metabolising enzymes remains.

Cimetidine was also originally thought to reduce hepatic blood flow, as measured by a reduction in the clearance of indocyanine green [13]. However, the validity of this method has been challenged as a decreased clearance of dye with cimetidine could also be the result of reduced hepatic extraction [31, 39, 40]. Cimetidine did not alter liver blood flow in other studies using the methods of sorbitol clearance [1], indocyanine green clearance [9,15] electromagnetic blood flowmetry [58] and ultrasound techniques [4].

Cimetidine has been shown to affect other cytotoxic drugs metabolised by microsomal enzyme systems in the liver. It increased the plasma half-life of hexamethylmelamine and drug toxicity in rats [19], increased the bone marrow toxicity of cyclophosphamide in mice [11] and caused a 3.8-fold rise in the doxorubicin area under the concentration-time curve (AUC) with a doubling of the elimination half-life in rabbits [5]. Pre-treatment with cimetidine has also increased the AUC of both oral and i.v. 5-fluorouracil in man [23].

In view of possible interactions through either modulation of gastric pH or inhibition of metabolising enzymes, the pharmacokinetics of both i.v. and oral etoposide were studied before and during the administration of cimetidine. In summary, the bioavailability of oral etoposide was investigated in three studies designed to assess (1) the effect of gastric emptying time, as modulated by metoclopramide or propantheline; (2) the effect of ethanol and the bile salt sodium tauroglycocholate; and (3)the effect of modification of stomach pH by cimetidine.

Patients and methods

Study I – the effect of gastric emptying time on the pharmacokinetics of oral etoposide

Patients. Seven patients receiving single-agent etoposide as chemotherapy for small-cell lung cancer were studied. Patients taking

opiate analgesics or antidepressants were excluded from the study, as were patients with glaucoma, symptoms of prostatism or ischaemic heart disease.

Treatment

Pharmacokinetic studies were performed on 2 days of each of two treatment cycles. The pharmacokinetics of oral etoposide was studied with and without metoclopramide during one course and with and without propantheline in the other. Patients entering this study had previously been studied after receiving i.v. etoposide (100 mg/m^2 infused over 2 h), with a total of 18 blood samples being collected over 24 h, from which the $AUC_{0-\infty}$ was used to calculate the bioavailability after oral dosing.

On each study day patients received two etoposide capsules (200 mg total dose) at between 900 and 1030 hours, immediately followed by two paracetamol capsules (1 g total dose), all taken with less than 200mls of tap water. Metoclopramide at 20 mg was given i.v. immediately before ingestion of etoposide and paracetamol. Oral propantheline at 60 mg was given 90 min before etoposide. The order in which patients received metoclopramide or propantheline as well as the day on which patients received etoposide with or without these agents was randomised.

Patients were fasted overnight and were allowed food and drink ad libitum at 3 h after oral etoposide administration. Patients were semi-supine for the first 3 h of the study and were not allowed paracetamol, opiate or anti-cholinergic drugs for 48 h before the study or during the study. Aspirin was used where patients required analgesia. The study was abandoned if patients required an opiate during the study or in the preceding 48 h. All other drugs were taken at least 4 h after the start of each study day. Most patients had the pharmacokinetic studies performed on successive days of two consecutive cycles (cycles were repeated every 21 days).

Study II – the effect of ethanol and sodium tauroglycocholate on the pharmacokinetics of oral etoposide

Patients

Six patients receiving single-agent chemotherapy with etoposide for small–cell lung cancer were studied. Patients were excluded from the study if they were taking drugs known to affect gastric emptying or small–bowel transit times. Patients acted as their own controls.

Treatment

Pharmacokinetic studies were performed over two days of two successive treatment cycles. The effect of ethanol was studied in one cycle and the effect of sodium tauroglycocholate in the other, in randomised order. The day of ethanol administration was also randomised, but the bile salt was always given on the 2nd of the study days in view of the theoretical subsequent contribution of this dose to the bile acid pool. Patients entering this study had previously been evaluated after receiving i.v. etoposide; from these data the $AUC_{0-\infty}$ was used to calculate oral bioavailability.

On each of the study days, patients received two etoposide capsules (200 mg total dose) at between 900 and 1030 hours with less than 200 ml of water. Ethanol was given in the form of 100 ml of a 20% solution (v/v) flavoured with a little sugar syrup. This solution was drunk by the patient during the 10 min following ingestion of the etoposide capsules. Sodium tauroglycocholate at 400 mg was given 10 min before etoposide in a hard gelatin capsule, the dissolution time of which was known to be approximately 20 min. Patients remained in the semi-supine position for the first 3 h of each study day and were fasted from midnight until 3 h post-dosing when food and drink were allowed ad libitum.

Study III – the effect of cimetidine on the pharmacokinetics of i.v. and oral etoposide

Patients

A total of 11 patients receiving single-agent etoposide as chemotherapy for small-cell carcinoma of the bronchus or relapsed non-Hodgkin's lymphoma or ovarian cancer were studied. Patients acted as their own controls. None had previously been treated with cimetidine and all had plasma creatinine levels of less than 130 μmol/l. Any patient receiving a drug of known interaction with hepatic drug metabolism was precluded from entry into the study.

Treatment

Pharmacokinetic studies were performed on 2 days of two successive treatment cycles. On the 1st day, patients received 150 mg of etoposide as an i.v. infusion over 1 h. On the 2nd day, after an overnight fast, patients received oral etoposide at 300 mg (three capsules) with up to 200 mls of water. On each study day, etoposide was given at between 900 and 1030 hours. No food or drink was permitted on the oral study day for 3 h after drug administration after which both were permitted ad libitum. Patients were requested to remain in the semi-supine position for the first 3 h following the oral dose of etoposide. After completion of the first pair of pharmacokinetics studies, patients were commenced on cimetidine at 400 mg b.i.d. Repeat pharmacokinetic studies after both i.v. and oral etoposide administration were performed not less than 3 weeks after the first. Cimetidine administration continued until completion of all the pharmacokinetic studies.

Sampling

On each study day, blood samples were withdrawn from an indwelling venous cannula at 0, 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 h. In the gastric emptying study, samples were also taken at 1.25 and 1.75 h because of the delayed peak plasma concentration on the day of propantheline administration. Plasma was separated by centrifugation at 1,200 g for 10 min and stored at -20°C until analysis.

Assay and pharmacokinetics

Etoposide

Plasma etoposide was measured using reverse-phase high-performance liquid chromatography (HPLC) with UV detection following solvent extraction [24]. Di-phenylhydantoin was used as the internal standard.

Paracetamol

Paracetamol was measured by HPLC with UV detection using a modification of the method described by Howie et al [28]. In all, 50 μl of the internal standard (3-acetaminophenol, 150 μg/ml) was added to 500 μl of plasma; then, 200 μl of 20% trichloroacetic acid was added and the tube was mixed well to precipitate the proteins.

Following centrifugation at 13,000 rpm for 5 min, 50 µl of supernatant was injected into the HPLC system. Separation was achieved on a 5-µm ODS column (Apex Hypersil, Jones Chromatography, Wales) with a mobile phase of water:acetic acid:ethyl acetate (98:1:1 by vol.). Detection was carned out by UV absorption at 240 nm. The limit of detection was 0.2 µg/ml, with both within and between run reproducibility of $< 10\%$ being observed at concentrations of 1.1, 6.2, and 19.5 µg/ml. Reproducibility at the limit of detection was $< 15\%$.

Pharmacokinetic parameters

When a pharmacokinetic study was performed on any day other than the 1st day of treatment, residual drug from the previous day was stripped from the measured concentrations on the study day using the formula:

$$\text{Actual } C_P^t = \text{Measured } C_P^t - C_P^0 \exp^{k_{el}t},$$

where C_P^t is the concentration in plasma at time t on the day of study and the term, $C_p^0 \exp^{k_{el}t}$ represents the residual drug concentration at time t from the previous dose, calculated from the plasma concentration at time 0 on the study day (C_P^0) and the elimination rate constant from the study day (k_{el}).

Pharmacokinetic parameters were derived using STRIPE, a model-independent interactive computer programme [36], as follows:

Area under the concentration-time curve (AUC): calculated according to the trapezoidal rule extrapolated out to infinity using the elimination rate constant

$$\textit{Elimination half-life } (t_{1/2}) = \frac{ln(2)}{\textit{Elimination rate constant}}$$

$$\textit{Absorption half-life} = \frac{ln(2)}{\textit{Absorption rate constant}}$$

$$\textit{Volume of distribution} = \frac{Dose}{AUC_{(0-00)} \times \textit{elimination rate constant}}$$

$$\textit{Clearance} = \frac{Dose}{AUC^{(0-00)}}$$

In the cimitidine study the bioavailability of oral drug during the treatment of patients with cimetidine was calculated in relation to the AUC of i.v. etoposide both before and during co-administration of cimetidine. Students paired t-test was used to compare etoposide pharmacokinetic parameters obtained with and without other agents.

Results

Study Ia – the effect of gastric emptying time: metoclopramide

Etoposide pharmacokinetic parameters obtained with and without the co-administration of metoclopramide are shown in Table 1. All patients tolerated the metoclopramide with no reported side effects. One patient was excluded from analysis as both etoposide and paracetamol absorption was very slow. On further investigation this patient was found to have previously had a vagotomy and pyloroplasty and to show symptoms of gastric stasis.

Table 1 Mean pharmacokinetic parameters recorded for etoposide alone and etoposide with metoclopramide (mean ± SD) (Paracetamol was co-administered on both occasions)

	Etoposide alone	Etoposide with metoclopramide
Absorption half-life (h)	0.31 + 0.26	0.31 + 0.42
Peak plasma concentration (mg/ml)	10.0 + 3.8	10.9 + 4.6
Time of peak plasma concentration (h)	1.3 + 0.9	1.1 + 0.9*
Elimination half-life (h)	7.0 + 2.5	6.6 + 1.4
AUC (mg ml^{-1} h)	68.4 + 20.3	74.3 + 25.9
Etoposide > 1 mg/ml (h)	15.8 + 4.1	17.7 + 4.5
Bioavailability (%)	61.7 + 12.7	66.2 + 14.9

* $P < 0.05$, Student's t-test

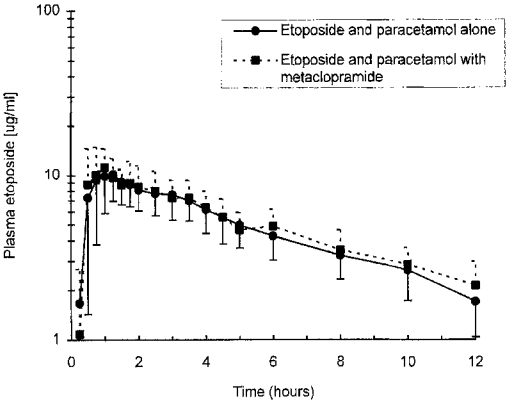

Fig. 1 Plasma etoposide against time after oral dosing with and without metaclopramide (mean with SD)

No statistically significant difference was found for any of the pharmacokinetic parameters of etoposide given alone or with metoclopramide. Figure 1 shows the pharmacokinetic profiles obtained for etoposide for the 2 days of the study and Fig. 2, the profiles for paracetamol. These graphs demonstrate that the mean curves are virtually superimposable for etoposide across the entire study period and for paracetamol from 1 h onwards. The inter-patient variation in the pharmacokinetic parameters of etoposide were similar on both days of the study. As with etoposide, there was no significant difference in the paracetamol $AUC_{(0-00)}$ (55.6 ± 22.1 µg ml^{-1} h alone vs 53.9 ± 18.9 µg ml^{-1} h with metoclopramide, $P = 0.40$) or t_{max} (1.6 ± 1.4 h alone versus 0.7 ± 0.4 h with metoclopramide; $P = 0.44$) when it was given with metoclopramide. Correlation coefficients between the paracetamol and etoposide AUC were 0.70 on the control study day and 0.80 on the metoclopramide study day, and those for t_{max} were 0.69 on the control day and 0.60 with metoclopramide.

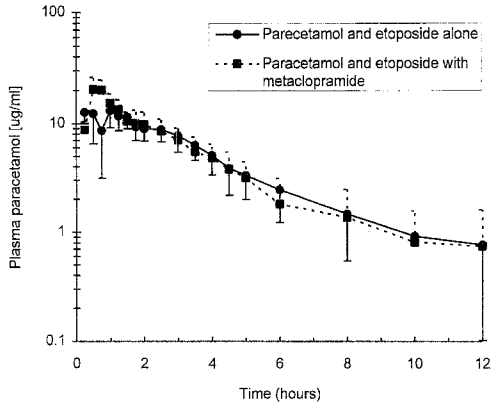

Fig. 2 Plasma paracetamol against time after oral dosing with and without metaclopramide (mean with SD)

Study Ib. the effect of gastric emptying time: Propantheline

Etoposide pharmacokinetic parameters are shown in Table 2 and plasma profiles, in Fig. 3. Plasma profiles obtained for paracetamol with and without propantheline are shown in Fig. 4. All patients experienced a dry mouth with the administration of propantheline and a lack of desire to pass urine during the first few hours after administration. No patient suffered urine retention, blurred vision or palpitations. The patient with delayed gastric emptying due to incomplete pyloroplasty was again excluded from this part of the study.

The bioavailability of etoposide was unchanged by the co-administration of propantheline, although the time to peak concentration was significantly delayed from 1.0 to 3.5 h for etoposide ($P = 0.007$) and from 1.1 to 3.0 h for paracetamol ($P = 0.009$). The paracetamol AUC was also unchanged by the addition of propantheline (60.8 ± 26.4 versus 56.4 ± 20.9 μg ml^{-1} h; $P = 0.11$). The absorption half-life of etoposide was significantly prolonged by propantheline, as was the duration of plasma concentration of etoposide exceeding 1 μg/ml, although by only 2.6 h. The correlation coefficients found between the AUC and t_{max} of etoposide and paracetamol were 0.92 and 0.52, respectively, on the control day and 0.23 and 0.77, respectively, with the co-administration of propantheline.

Study IIa – The effect of ethanol on etoposide bioavailability.

Pharmacokinetic parameters are shown in Table 3. The ethanol solution contained 20 mls of ethanol, a dose roughly equivalent to a large sherry or 2/6 gill of spirits. The ethanol solution was well tolerated by all patients and enjoyed by most. Ethanol did not affect the pharmacokinetics of oral etoposide and particularly had no effect on the AUC or the variability in bioavailability.

Table 2 Mean pharmacokinetic parameters recorded for etoposide alone and etoposide with propantheline (mean ± SD) (Paracetamol was co-administered in both cases)

	Etoposide alone	Etoposide with propantheline
Absorption half-life (h)	0.17 + 0.08	0.77 + 0.63**
Peak plasma concentration (mg/ml)	11.3 + 3.5	9.9 + 4.5
Time of peak plasma concentration (h)	1.1 + 0.4	3.5 + 2.0**
Elimination half-life (h)	6.9 + 3.1	6.3 + 1.4
AUC (mg ml^{-1} h)	78.3 + 19.1	88.1 + 23.6
Etoposide > 1 mg/ml (h)	17.6 + 3.5	20.2 + 2.8**
Bioavailability (%)	69.7 + 12.1	79.1 + 14.9

* $P < 0.01$, Student's t-test

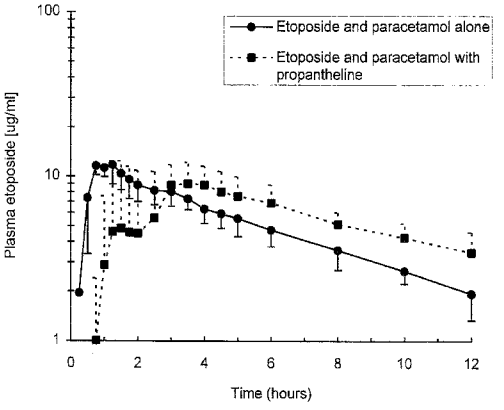

Fig. 3 Plasma etoposide against time after oral dosing with and without propantheline (mean with SD)

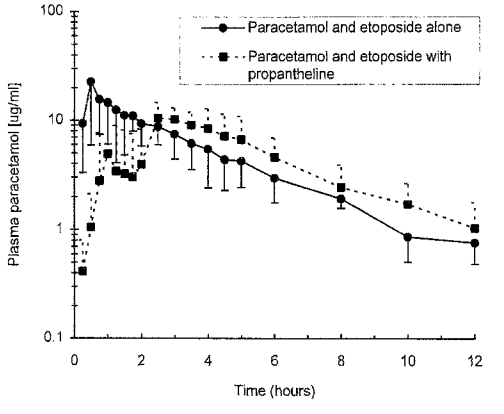

Fig. 4 Plasma aracetamol against time after oral dosing with and without propantheline (mean with SD)

Study IIb – The effect of sodium tauroglycocholate on etoposide bioavailability.

Pharmacokinetic parameters are shown in Table 4. The capsules of sodium tauroglycocholate were tolerated well by all patients. The pharmacokinetics of etoposide was not influenced by the co-administration of sodium

Table 3 Mean pharmacokinetic parameters recorded for etoposide alone and etoposide with ethanol[a] (mean ± 5D)

	Etoposide alone	Etoposide with ethanol
Absorption half-life (h)	0.20 + 0.06	0.33 + 0.39
Peak plasma concentration (mg/ml)	9.4 + 4.2	9.6 + 4.4
Time of peak plasma concentration (h)	1.3 + 0.7	1.6 + 0.7
Elimination half-life (h)	7.0 + 1.5	7.2 + 1.2
AUC (mg ml^{-1} h)	68.9 + 22.1	70.6 + 23.9
Bioavailability (%)	62.2 + 14.0	64.5 + 18.9

[a] No significant difference

Table 4 Mean pharmacokinetic parameters recorded for etoposide alone and etoposide with sodium tauroglycocholae[a] (*STC* (mean ± SD))

	Etoposide alone	Etoposide with STC
Absorption half-life (h)	0.30 + 0.30	0.33 + 0.60
Peak plasma concentration (mg/ml)	8.9 + 5.1	11.3 + 4.8
Time of peak plasma concentration (h)	1.6 + 1.4	1.4 + 1.8
Elimination half-life (h)	7.8 + 3.2	7.9 + 1.6
AUC (mg ml^{-1} h)	65.0 + 29.1	71.2 + 16.7
Bioavailability (%)	57.8 + 22.9	65.2 + 8.8

[a] No significant difference

tauroglycocholate, although the variability in bioavailability was reduced from 57.8 ± 22.9% when etoposide was given alone to 65.2 ± 8.8% when it was given with the bile salt.

Study III – The effect of cimetidine

Intravenous etoposide

Mean pharmacokinetic data obtained for the 11 patients are shown in Table 5. There was no change in any of the pharmacokinetic parameters of etoposide as measured before and during the co-administration of cimetidine.

Oral etoposide

The mean pharmacokinetic data obtained for the ten patients studied are shown in Table 6. One patient was in partial bowel obstruction at the time of the first oral study and was therefore excluded from the analysis of oral pharmacokinetic parameters. Both the drug AUC and the bioavailability of etoposide were unchanged by the administration of cimetidine. The inter-patient variation in AUC following oral administration was 35–40%, considerably greater than the figure of 20–25% recorded for i.v. etoposide.

Table 5 Pharmacokinetic data obtained for i.v. etoposide at 150 mg before and during the administration of cimetidine in 11 patients (mean ± SD)[a]

	Pre-cimetidine	Post-cimetidine
$t_{1/2}$ (h)	6.9 ± 1.3	6.5 ± 1.3
AUC (μg ml^{-1} h)	87.9 ± 17.0	89.1 ± 23.6
Vd (l/m^2)	10.1 ± 2.1	8.9 ± 1.9
Cl (ml min^{-1} m^{-2})	17.8 ± 5.2	16.4 ± 5.6

[a] No significant differences

Table 6 Pharmacokinetic data obtained for oral etoposide at 300 mg before and during the administration of cimetidine in 10 patients (mean ± SD)[a]

	Pre-cimetidine	Post-cimetidine
$t_{1/2}$ (h)	7.4 ± 1.0	8.3 ± 1.5
AUC (μg ml^{-1} h)	106.6 ± 37.9	104.2 ± 43.7
Bioavailability (%)	61.6 ± 17.1	53.0 ± 13.4
Bioavailability on pre-cimetidine i.v. AUC (%)	–	56.0 ± 17.3
Cmax (μg/ml)	13.9 ± 5.8	11.6 ± 3.8
*T*max (h)	1.7 ± 1.0	1.6 ± 1.0

[a] No significant differences

Discussion

Although administration of etoposide in the oral form is more common now than earlier in its clinical history, a frustrating obstacle in its use is the incomplete and variable bioavailability. Although the metabolism of etoposide is poorly understood and first-pass metabolism in the liver after oral dosing remains a possibility, the poor solubility of etoposide and its limited stability in gastric and intestinal fluids is likely to result in incomplete absorption and reduced bioavailability. Simple pharmacological methods that improve stability and bioavailability would make the oral route of administration more reliable, which may be particularly relevant in prolonged dosing schedules.

The first of the series of studies described in this paper represents an attempt to improve the bioavailability of oral etoposide by modulating the concentration (and thereby the stability) of etoposide in the small intestine by modifying the rate at which etoposide is emptied from the stomach. The effect of metoclopramide (a commonly used anti-emetic drug in oncology practice) in increasing the rate of gastric emptying has been most readily demonstrated in patients investi-

gated for gastrointestinal symptoms [8, 18, 32, 46]. Although two studies have shown a more rapid stomach emptying in normal subjects after a liquid drink [2, 14], a third study failed to do so after a solid meal [18]. In addition to its effect on the stomach, metoclopramide reduces small bowel transit time [17, 27]. By virtue of this effect on the gut, metoclopramide has been shown to alter drug absorption. In patients known to be slow absorbers of paracetamol, metoclopramide significantly increased the peak plasma concentration and reduced the time to peak of paracetamol, but without changing the AUC [46]. Metoclopramide reduced the steady-state serum levels of digoxin when the latter was given as a large-particle-size tablet with a slow dissolution rate [8, 42]. A recent study has reported that metoclopramide increases the oral bioavailability of TCNU, a nitrosourea [59].

In this study metoclopramide was shown not to affect the pharmacokinetics of oral etoposide. This would suggest that the oral formulation of etoposide is emptied rapidly from the stomach in most subjects and that metoclopramide cannot speed this further. Metoclopramide also had no effect on the AUC or t_{max} of paracetamol. In a wider context this finding demonstrates that the co-administration of oral etoposide and metoclopramide, likely to occur in clinical practice, has no effect on oral etoposide bioavailability.

The slowing of gastric emptying time by propantheline has been well established for i.v. drug [14, 46], and three studies have shown a similar effect with oral propantheline [6, 29, 30]. In five fasting normal volunteers, oral propantheline increased the average small-bowel transit time from 40 to 94 min [12]. Propantheline has been shown to affect the absorption of several drugs. When given prior to paracetamol, it reduced the peak plasma concentration and extended the time to peak from 70 to 160 min, but without affecting the AUC [46]. Oral administration of small doses of propantheline increased the steady–state levels of digoxin, but only when the latter was formulated in large particles in a tablet of slow dissolution time [21, 34]. Absorption of digoxin in a liquid preparation was unaffected by propantheline [42]. Propantheline increased the bioavailability of atenolol and delayed the Cmax from 2.1 to 4.5 h [50].

In the study reported herein propantheline had a profound effect on etoposide absorption, delaying the peak plasma concentration from 1.1 h on the control day to 3.5 h when the two drugs were given together. Despite this delayed release from the stomach, resulting in slower absorption, etoposide AUC and bioavailability were not improved. It is, however, noteworthy that over the 4 days of this study (etoposide with and without metoclopramide and with and without propantheline) both the mean AUC and bioavailability were highest on the day on which patients received propantheline. Our failure to demonstrate a significant effect of propantheline may have been due to the small numbers of patients enrolled in the study.

The effect of propantheline on gastric emptying is confirmed by the paracetamol data, which similarly demonstrate a significant prolongation of t_{max} from 1.1 to 3.0 h, but no effect on the paracetamol AUC. Paracetamol is used as a marker of gastric emptying time as its absorption from the stomach is virtually nil. The close agreement found between the times of the peak plasma concentration of etoposide and paracetamol and in the plasma profiles of the two compounds given with and without metoclopramide and propantheline suggests that etoposide is also absorbed in the upper small intestine, with little absorption from the stomach.

The second study reported herein demonstrated that neither the co-administration of ethanol nor that of sodium tauroglycocholate improved the bioavailability of etoposide. The greater stability of etoposide in solution demonstrated in vitro with these agents has thus not been translated into improved bioavailability in vivo. Either the stability of etoposide is not an important factor with regard to absorption or the wrong dose of ethanol or sodium tauroglycocholate was used. Additionally, although there was a marked improvement in the stability of etoposide in the in vitro study over the 8-h study period [33], this improvement was much less marked over the first 60–90 min of incubation, which is the more important period in terms of in vivo absorption. It is possible that both ethanol and sodium tauroglycocholate would improve the absorption of etoposide if they were mixed with etoposide prior to administration. In clinical practice this would make it necessary to use the unpalatable i.v. preparation of etoposide for oral use. These results are disappointing since the addition of tauroglycocholate was found to enhance the absorption rate of podophyllin in isolated rat intestinal loops [37], possibly due to reduced resistance to absorption by the intestinal mucus barrier.

In the third study, cimetidine was shown not to interact with either oral or i.v. etoposide. The oral absorption of etoposide is not improved by decreasing stomach acidity, which should improve drug stability in the gastric environment. This probably reflects that in most patients, etoposide is emptied from the fasted stomach before significant loss of stability and solubility occurs. Alternatively, the resting pH in the gastric fluid of these fasted patients may have been sufficiently high before cimetidine was given, such that etoposide stability in the stomach was already assured.

Experiments employing isolated rat- and mouse-liver microsomes have demonstrated the formation of the 3',4' dihydroxy derivative of etoposide, a process that is cytochrome P450 system-dependent [16, 41]. There is also evidence that this metabolite is cytotoxic [41], and it is therefore possible that the cytotoxicity of etoposide is partly related to the metabolic activation

of the drug to this derivative. This metabolite has not been detected in humans, although it is likely that reactivity would mean that it would be very short-lived. If this is an important pathway in the activation of etoposide, then an interaction with cimetidine may be relevant at the cellular level, and this interaction would not be apparent in the study reported herein.

The conclusions of this series of studies is that none of the approaches resulted in a significant change in the bioavailability of etoposide. The only significant modification in etoposide pharmacokinetics occurred after the administration of propantheline, which significantly delayed the time to t_{max} by its effect on gastric emptying. One result of this delayed peak was a significant increase in the period over which plasma etoposide concentrations exceeded 1 μg/ml ($P = 0.008$). We have recently suggested that the prolonged maintenance of low concentrations of etoposide is important in determining cytotoxic activity, but it is unlikely that the advantage gained would warrant the routine co-administration of propantheline to patients receiving oral etoposide. That none of the agents studied significantly altered the bioavailability of etoposide suggests that they can be safely given together without compromising drug activity. It is also noteworthy that the oral dose of etoposide employed in these studies was 200–300 mg, and the oral bioavailability of etoposide has been shown to be dependent on dose [54]. Although with prolonged administration schedules the dose is normally only 50–100 mg, higher oral doses were employed in this study because the lower bioavailability at these higher doses may be related to loss of stability. Thus, any effect of using modulating agents to improve bioavailability may not be as effective at lower doses where bioavailability is already higher. Conversely, although these agents did not influence the bioavailability of etoposide in this study at doses of 200–300 mg, an effect may exist at lower doses of etoposide if stability is the factor limiting bioavailability.

The absorption of etoposide is likely to depend on a number of interacting factors, the separation of which may be difficult. Neither gastric emptying time nor modification of the solvent environment was shown in these studies to be a major factor determining the bioavailability of etoposide. Despite the failure of these studies to demonstrate an improvement in etoposide stability and, thereby, bioavailability, it remains likely that a major factor in the poor and variable absorption of etoposide after oral administration is its instability in the gastric and intestinal environment. A water-soluble etoposide preparation, currently under evaluation [43], would be expected to have improved stability and, thus, increased bioavailability. A significant improvement in the absorption of etoposide, together with a reduction in day-to-day variability, remains an important objective in the clinical use of oral etoposide.

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