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# The influence of cimetidine on the pharmacokinetics of 5-fluorouracil

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**1** The influence of cimetidine pretreatment on the pharmacokinetics of 5-fluorouracil (5FU) has been studied in 15 ambulant patients with carcinoma.
**2** Neither pretreatment with a single dose of cimetidine (400 mg) nor with daily treatment at 1000 mg for 1 week altered 5FU pharmacokinetics.
**3** Pretreatment with cimetidine for 4 weeks (1000 mg daily) led to increased peak plasma concentrations of 5FU and also area under the plasma concentration-time curve (AUC). The peak plasma concentration after oral 5FU was increased by 74% from 18.7 ± 4.5 μg/ml (mean ± s.e. mean) to 32.6 ± 4.4 μg/ml ($P < 0.05$) and AUC was increased by 72% from 528 ± 133 μg $ml^{-1}$ min (mean ± s.e. mean) to 911 ± 152 μg $ml^{-1}$ min ($P < 0.05$). After intravenous 5FU, AUC was increased by 27% from 977 ± 96 μg $ml^{-1}$ min (mean ± s.e. mean) to 1353 ± 124 μg $ml^{-1}$ min ($P < 0.01$). Total body clearance for 5FU following intravenous administration was decreased by 28% from 987 ± 116 ml/min (mean ± s.e. mean) to 711 ± 87 ml/min ($P < 0.01$).
**4** The elimination half-life of 5FU was not altered by cimetidine.
**5** The basis of the interaction between 5FU and cimetidine is uncertain but probably a combination of inhibited drug metabolism and reduced liver blood flow. The therapeutic implications are considerable and additional care should be taken in patients receiving the two drugs concomitantly.

**Keywords** cimetidine 5-fluorouracil pharmacokinetics interaction

## Introduction

5-fluorouracil (5FU) is widely used in the treatment of several malignancies, particularly breast, stomach and colon carcinoma (Murinson & Myers, 1978). It is the most active single agent in cancers of the large bowel (Livingston & Carter, 1970). 5FU may be administered either orally or parenterally. The bioavailability of the drug after oral administration varies considerably both between patients (28%–100%) (Cohen *et al.*, 1974; Finn & Sadee, 1975; Murinson & Myers, 1978; Phillips *et al.*, 1980) and within patients (Finch *et al.*, 1979). Several factors may contribute to poor bioavailability. 5FU is a basic drug with a pKa of 8.1 (Dorr & Fritz, 1980) and is therefore predominantly ionised, not only at the low gastric pH but also at normal duodenal pH. This would tend to decrease its absorption (Murinson & Myers, 1978) and indeed Cohen *et al.* (1974) showed greater absorption occurred using water or bicarbonate buffer (pH 9) as the diluent rather than orange juice (pH 4) as recommended by the manufacturer. Alternatively a high hepatic extraction ratio or first pass effect may be responsible (Cohen *et al.*, 1974; Finn & Sadee, 1975; Murinson & Myers, 1978), though theoretical considerations have suggested that this may not be as high as previously thought (Collins *et al.*, 1980). 5FU may be considered a pro-drug, metabolic activation to fluorinated

nucleosides and nucleotides being essential for cytotoxic activity (Chabner, 1982). Several drugs, including some cytotoxics (methotrexate, misonidazole and thymidine) have been shown to interact with 5FU modifying the extent of activation of catabolism (Schilsky *et al.*, 1981; Chabner, 1982; McDermott *et al.*, 1983).

Cimetidine, a potent histamine $H_2$-receptor antagonist, has several actions which might potentially improve the bioavailability of 5FU (Schwinghammer, 1981). Inhibition of gastric acid secretion by cimetidine increases the pH both of the gastric and duodenal contents (Freston, 1982) which may lead to improved absorption. Further, cimetidine has increased the bioavailability of several orally administered drugs including propranolol (Feely *et al.*, 1981; Heagerty *et al.*, 1981; Reimann *et al.*, 1981), warfarin (Serlin *et al.*, 1979), theophylline (Jackson *et al.*, 1981; Reitberg *et al.*, 1981), diazepam (Klotz & Reiman, 1981) and phenytoin (Neuvonen *et al.*, 1981). This effect is thought to be largely due to inhibition of liver microsomal oxidative systems (Henry *et al.*, 1980; Puurunen *et al.*, 1980; Knodell *et al.*, 1982) but a decrease in hepatic blood flow may contribute (Feely *et al.*, 1981, 1982). Since 5FU is degraded largely by intermediary cellular metabolism (dihydrouracil dehydrogenase) (Chabner, 1982) rather than xenobiotic metabolism the reduction in hepatic blood flow has the greater potential to affect the pharmacokinetics of 5FU.

The following studies were performed to determine the influence of cimetidine on the pharmacokinetics of 5FU and in particular whether the oral bioavailability of 5FU could be improved by the use of cimetidine.

## Methods

The study was approved by the local ethical committee.

### *Patients*

Ten patients with advanced colon cancer and five patients with malignant mesothelioma receiving 5FU, as a single agent, in the Department of Medical Oncology were studied. Two patients participated in each of two investigations. Patients acted as their own controls. Anti-emetic therapy was not required and no patient was receiving additional medication. Although ambulant, patients remained supine for the duration of blood sampling to remove the effects of position on hepatic blood flow.

### *Drug administration*

5FU was administered at a dose of 15 mg/kg daily for 5 days and repeated every 4 weeks. Oral doses were administered in orange squash (20% v/v, 100 ml) at pH 4.5. Patients were fasted overnight prior to the oral dosing. Intravenous doses were given by bolus injection.

Toxicity of treatment was assessed by patient symptoms and haematological profile prior to each treatment course.

*1) Single dose cimetidine study* Five patients (four with colonic cancer and one with malignant mesothelioma) were studied and administration was as follows:

Day 1 5FU orally
Day 2 Cimetidine 400 mg orally 90 min prior to oral 5FU administration
Day 3 5FU by i.v. injection

*2) Prolonged cimetidine administration* Twelve patients (seven with colonic cancer and five with malignant mesothelioma) were studied during the first 2 days of two consecutive cycles of therapy. 5FU was administered orally on Day 1 and intravenously on Day 2 of each cycle of therapy. The second cycle was preceded by cimetidine (200 mg thrice daily and 400 mg at night) for 1 week in six patients and for 4 weeks in a further six patients (Figure 1).

### Sampling

Blood samples (10 ml) were collected into lithium heparin tubes at the following times after 5FU administration: 0, 2.5, 5, 7.5, 10, 15, 20, 30 and 45 min and 1, 1.3, 1.6, 2, 2.5, 3 and 4 h. The plasma samples were then separated and stored frozen at −20°C prior to assay.

### *Assay*

Plasma samples were analysed by gas liquid chromatography using a nitrogen detector as previously described (Finch *et al.*, 1979). The maximum sensitivity of this assay was 1 μg/ml plasma. The assay is specific for 5FU in the presence of cimetidine.

### *Statistics*

The pharmacokinetic analysis was performed using an interactive computer program, STRIPE (Johnston & Woollard, 1983). This program

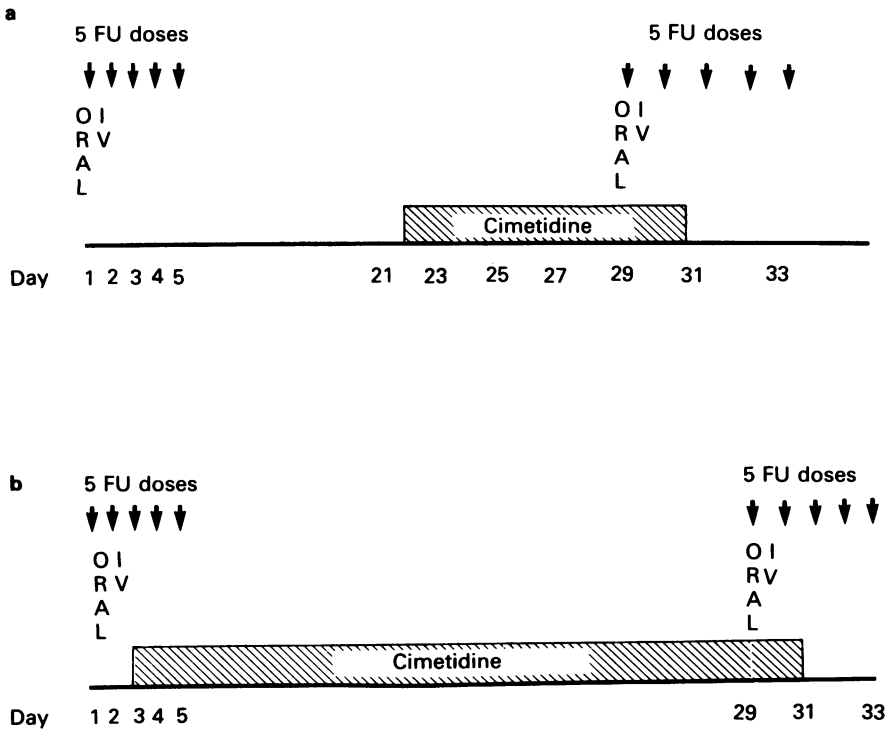


**Figure 1** Treatment plan for patients receiving prolonged pretreatment with cimetidine a) pretreatment for 1 week and b) pretreatment for 4 weeks.

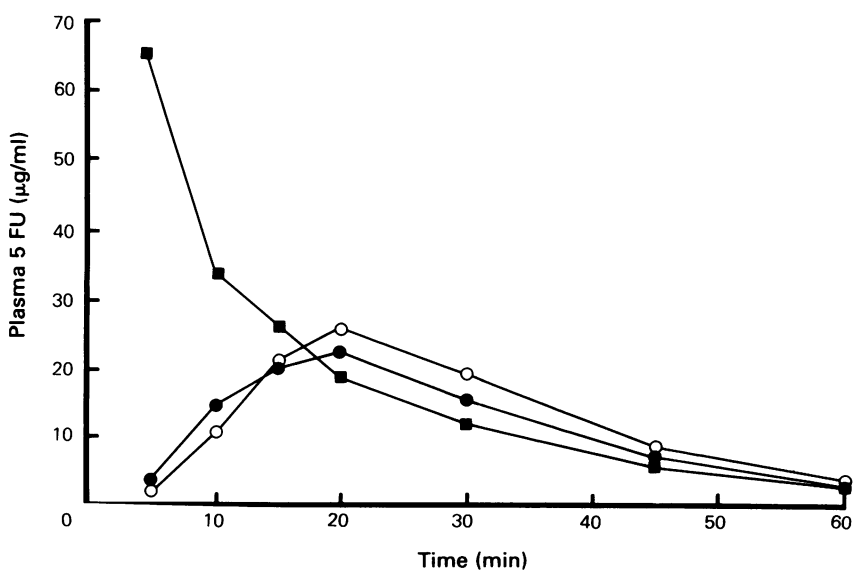


**Figure 2** Mean plasma concentrations of 5FU following i.v. (■——■) and oral administration with (○——○) and without (●——●) preceding cimetidine, as a single dose (400 mg).

calculated AUC by the trapezoidal method and extrapolated to infinity. The elimination half-life of 5FU in plasma ($t_{½,z}$) was derived from the equation, $0.693/\lambda_z$ ($\lambda_z$ = elimination rate constant); the apparent volume of distribution ($V$) from the relationship, Dose/AUC × $k$ and the total body clearance (CL) from the relationship, Dose/AUC. Apparent bioavailability is defined as the ratio $AUC_{oral}/AUC_{intravenous}$ expressed as a percentage. The bioavailability for oral 5FU following pretreatment with continuous cimetidine for 1 or 4 weeks was calculated using the intravenous AUC also after pretreatment with cimetidine.

Student's $t$-test was used for statistical analysis.

## Results

*1) Single dose cimetidine study*

The absorption of oral 5FU was not improved by a single dose of cimetidine. The plasma concentration profiles of 5FU following i.v. and oral administration with and without the preceding dose of cimetidine are shown in Figure 2. The pharmacokinetic data are shown in Table 1. Cimetidine given as a single dose 90 min before oral 5FU did not alter the peak plasma concentrations, elimination half life, AUC (Figure 3a) or bioavailability of 5FU.

*2) Prolonged cimetidine administration*

*1 week pretreatment with cimetidine* Administration of cimetidine for 1 week did not affect the plasma concentrations of 5FU following i.v. or oral administration. The plasma concentrations of 5FU are shown following i.v. and oral treatment in Figure 4 and the pharmacokinetic data in Table 2. None of these data was influenced by cimetidine (Figure 3b and 5a).

*4 week pretreatment with cimetidine* In a further study pretreatment with cimetidine for 4 weeks produced significant alterations to the 5FU plasma concentrations achieved (Figures 6, 7 and Table 3). After oral 5FU the mean increase in peak plasma concentrations was 74% and of AUC was 72% (Figure 3c). The change in bioavailability was not significant. After intravenous 5FU a mean increase in AUC of 27% was produced by cimetidine (Figure 5b) and the mean reduction in total body clearance was 28%. The elimination half life was not altered.

There was no apparent increase in the toxicity of treatment subsequent to these increased concentrations of 5FU.

## Discussion

Oral 5FU has been widely used, particularly in the treatment of gastrointestinal cancer, but has generally been considered less effective than 5FU administered intravenously (Stolinsky *et al.*, 1975; Ansfield *et al.*, 1977; Murinson & Myers, 1978). This could be accounted for, at least in part, by poor bioavailability following oral administration (Murinson & Myers, 1978; Phillips *et al.*, 1980). The possibility that cimetidine could improve bioavailability by several differing actions (Feely *et al.*, 1981; Somogyi & Gugler, 1982) prompted the studies presented here. Our observations have shown that whilst pretreatment with cimetidine for 4 weeks altered 5FU pharmacokinetics, pretreatment with a single dose or for 1 week was without effect.

Single doses of cimetidine have been shown to inhibit both basal and stimulated gastric acid secretion and to increase gastric pH, this effect being maximal at 90 min (Freston, 1982). Furthermore prolonged administration regularly results in increase in both gastric and duodenal pH (Freston, 1982). Thus despite the

**Table 1** Mean data ± s.e. mean following administration of 5FU 15 mg/kg intravenously, orally, or orally after a single dose of cimetidine (400 mg)

| | *i.v.* | *Oral* | P *value* | *Oral after cimetidine* |
|---|---|---|---|---|
| $C_{max}$ (μg/ml) | – | 25.1 ± 6.1 | NS | 28.6 ± 8.3 |
| Absorption $t_{½}$ (min) | – | 5.1 ± 1.0 | NS | 5.8 ± 1.0 |
| Elimination $t_{½,z}$ (min) | 12.7 ± 1.5 | 10.6 ± 0.9 | NS | 10.8 ± 1.3 |
| $AUC_{0-\infty}$ (μg $ml^{-1}$ min) | 1569 ± 305 | 698 ± 137 | NS | 802 ± 203 |
| Clearance (ml/min) | 712 ± 144 | – | | – |
| Volume of distribution (l) | 11.9 ± 1.4 | – | | – |
| Bioavailability (%) | – | 45 ± 3 | NS | 53 ± 12 |

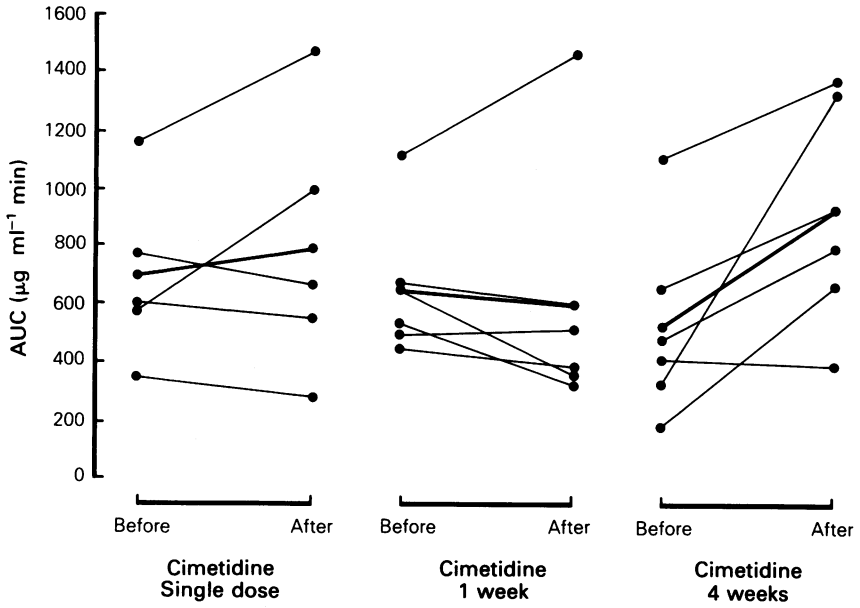


**Figure 3** AUC for individual patients (●——●), together with the mean (●——●), following oral 5FU before and after cimetidine pretreatment for a) one dose, b) 1 week and c) 4 weeks.

fact that gastric and duodenal pH were not measured in this study, it can be reasonably assumed that the pH was increased, probably with the single dose, but certainly following continuous treatment with cimetidine for 1 week. This might have been expected to improve absorption of 5FU by decreasing the degree of ionisation of this highly basic drug (pKa 8.1) (Dorr & Fritz, 1980). The failure of cimetidine to enhance the absorption of 5FU is in contrast to the data from Cohen *et al.* (1974) who showed a significant increase in bioavaila-

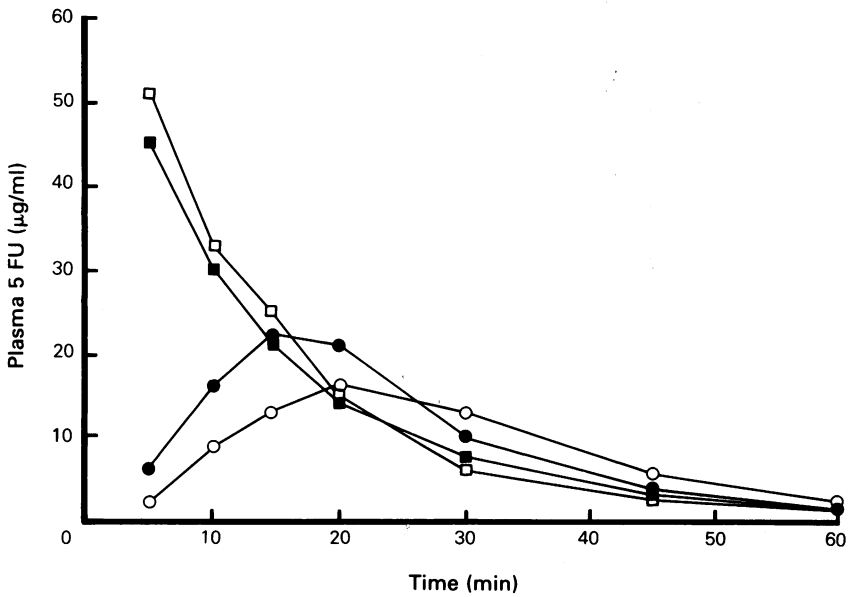


**Figure 4** Mean plasma concentrations of 5FU before (closed symbols) and after (open symbols) pretreatment with cimetidine for 1 week following oral (●——●, ○——○) and intravenous (■——■, □——□) administration.

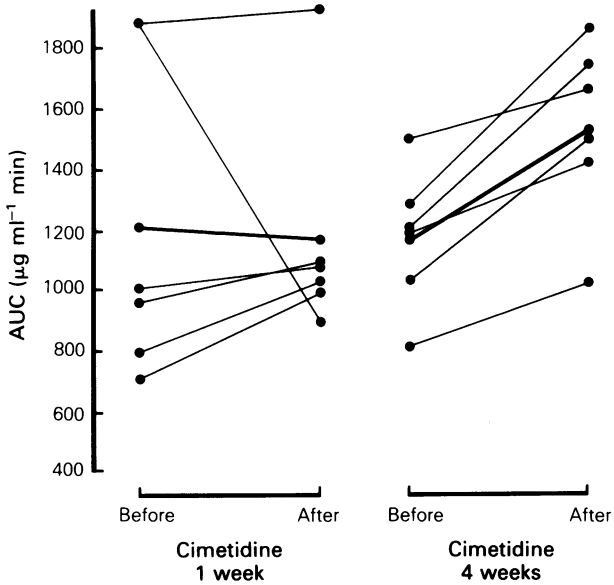


**Figure 5** AUC for individual patients (•——•), together with the mean (•——•), following i.v. 5FU before and after cimetidine pretreatment for a) 1 week and b) 4 weeks.

bility when 5FU was administered in a bicarbonate vehicle (pH 9) and in water compared with the administration in orange juice (pH4) in two out of three patients. However in the third patient bioavailability was lowest with the bicarbonate buffer. The small number of patients studied and the inherent interpatient variability may have accounted for the differences between these two studies. It seems unlikely from our data that low gastric or duodenal pH is responsible for poor absorption of 5FU.

Cimetidine has a profound effect on the hepatic metabolism of many drugs (Puurunen *et al.*, 1980; Feely *et al.*, 1981; Somogyi & Gugler, 1982). In addition animal studies have shown that cimetidine can enhance the antitumour activity of cyclophosphamide approximately two-fold (Dorr & Alberts, 1982), an effect presumed to be due to greater concentrations of active metabolites. Increased plasma concentrations of drugs given with cimetidine have been attributed to both inhibition of hepatic microsomal metabolism (Henry *et al.*, 1981;

**Table 2** Mean data ± s.e. mean following administration of 5FU 15 mg/kg intravenously or orally before and after 1 week's treatment with cimetidine (1000 mg daily)

| | *i.v. before cimetidine* | P *value* | *i.v. after cimetidine for 1 week* |
|---|---|---|---|
| Elimination $t_{½,z}$ (min) | 10.2 ± 0.7 | NS | 9.9 ± 1.1 |
| $AUC_{0-\infty}$ (μg ml$^{-1}$ min) | 1213 ± 217 | NS | 1172 ± 156 |
| Clearance (ml/min) | 892 ± 154 | NS | 849 ± 78 |
| Volume of distribution (l) | 13.4 ± 2.6 | NS | 12.1 ± 1.8 |
| | *Oral before cimetidine* | P *value* | *Oral after cimetidine for 1 week* |
| $C_{max}$ (μg/ml) | 22.5 ± 4.4 | NS | 20.0 ± 6.9 |
| Absorption $t$ (min) | 4.1 ± 0.7 | NS | 4.7 ± 0.6 |
| Elimination $t_{½,z}$ (min) | 8.2 ± 0.7 | NS | 9.6 ± 1.1 |
| $AUC_{0-\infty}$ (μg ml$^{-1}$ min) | 561 ± 100 | NS | 517 ± 174 |
| Bioavailability (%) | 48 ± 4 | NS | 40 ± 7 |

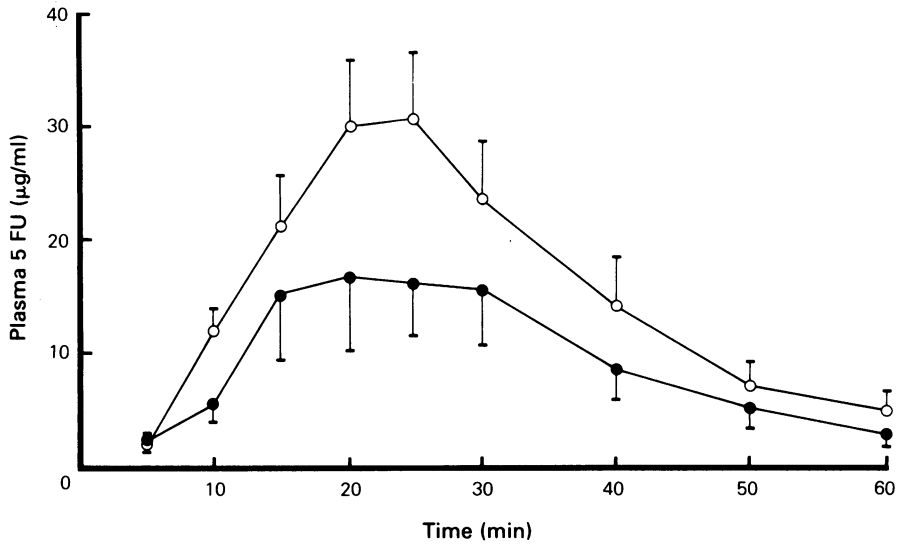


**Figure 6** Mean plasma concentrations of 5FU following oral administration before (●——●) and after (○——○) cimetidine for 4 weeks.

Puurunen *et al.*, 1980; Knodel *et al.*, 1982) and to reduced hepatic blood flow (Feely *et al.*, 1981, 1982). The imidazole ring of cimetidine is thought to be responsible for the interaction with one or more forms of cytochrome P450, thus modifying metabolism of other drugs by the mixed function oxidase system (Somogyi & Gugler, 1982). The metabolism of 5FU by dihydrouracil dehydrogenase, a cytoplasmic enzyme (Chabner, 1982), should not be affected by microsomal inhibition. Despite this Messiha & Hughes (1979) have shown that the cytoplasmic enzymes, alcohol dehydrogenase and aldehyde dehydrogenase, may be inhibited by histamine $H_2$-receptor antagonists, and that the effects are complex. In concert with this, Feely & Wood (1982) have shown increased plasma concentrations of ethanol in patients pretreated with cimetidine for 1 week. Additional evidence of an effect of other drugs on the

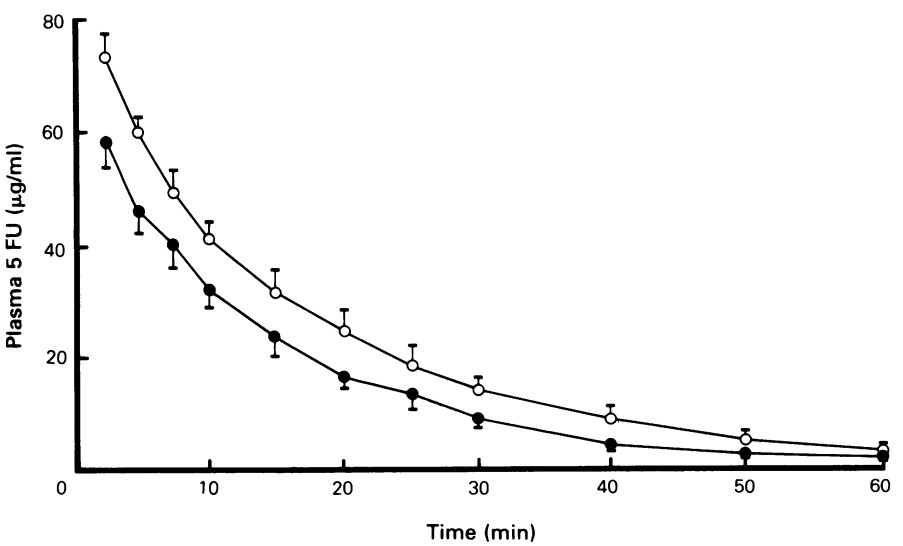


**Figure 7** Mean plasma concentrations of 5FU following i.v. administration before (●——●) and after (○——○) cimetidine for 4 weeks.

**Table 3** Mean data ± s.e. mean following administration of 5FU 15 mg/kg intravenously and orally before and after 4 weeks' cimetidine therapy (1000 mg daily)

| | *i.v.* | P *value* | *i.v. after cimetidine for 4 weeks* |
|---|---|---|---|
| Elimination $t_{½,z}$ (min) | 10.6 ± 0.8 | NS | 11.8 ± 1.2 |
| $AUC_{0-\infty}$ (μg $ml^{-1}$ min) | 977 ± 96 | < 0.01 | 1353 ± 124 |
| Clearance (ml/min) | 987 ± 116 | NS | 711 ± 87 |
| Volume of distribution (l) | 15.6 ± 2.1 | NS | 12.5 ± 0.9 |
| | *Oral* | P *value* | *Oral after cimetidine for 4 weeks* |
| $C_{max}$ (μg/ml) | 18.7 ± 4.5 | < 0.05 | 32.6 ± 4.4 |
| Absorption *t* (min) | 4.2 ± 0.6 | NS | 4.5 ± 0.4 |
| Elimination $t_{½,z}$ (min) | 10.5 ± 0.8 | NS | 10.7 ± 1.3 |
| $AUC_{0-\infty}$ (μg $ml^{-1}$ min) | 528 ± 133 | < 0.05 | 911 ± 152 |
| Bioavailability (%) | 55 ± 12 | NS | 66 ± 7 |

metabolism of 5FU is provided by the observation that concomitant misonidazole leads to increased 5FU plasma concentrations (McDermott *et al.*, 1983). Although the mechanism of this interaction is unclear it is of interest that cimetidine and misonidazole share the imidazole ring structure.

Cimetidine may also influence the metabolism of drugs via reduction in hepatic blood flow (Feely *et al.*, 1981, 1982; Somogyi & Gugler, 1982). Hepatic blood flow is considered a major determinant of hepatic clearance for highly extracted drugs after i.v. administration, while metabolising activity of the liver is the major determinant after oral administration (Wilkinson & Shand, 1975). In addition to its effect on hepatic blood flow, cimetidine influences the blood flow of other gastrointestinal organs (Schwinghammer, 1981). It is possible that this action may be as important as that on hepatic blood flow, in view of the presence of dihydrouracil dehydrogenase in the gastrointestinal mucosa and the suggestions that hepatic clearance may contribute less to 5FU elimination than was previously thought (Collins *et al.*, 1980; Chabner, 1982). The enhancement of 5FU levels after both i.v. and oral administration suggests a combination of factors may be responsible. Following oral 5FU the increase in peak plasma concentrations and AUC without a change in the elimination half-life can be explained by reduced first-pass extraction. After intravenous 5FU the elimination half-life showed a tendency to increase (increased in four patients, unchanged in one patient and decreased in one patient) but this did not achieve statistical significance.

The studies reported here suggest that the duration of pretreatment with cimetidine may be critical. Several workers have shown that the rate of microsomal enzyme inhibition or alteration in hepatic blood flow can be rapid (Puurunen *et al.*, 1980; Feely *et al.*, 1982; Speeg *et al.*, 1982). Thus, for example, a single dose of cimetidine resulted in increased propranolol plasma concentrations, though this effect was intensified after a week (Reimann *et al.*, 1981). Speeg *et al.* (1982) have shown a rapid onset of effect, but no intensification over the following 4 weeks. Feely *et al.* (1981) showed reduction in liver blood flow of almost 25% after a single dose and of 33% after a week. More prolonged observations have not been reported. In the present study the effect on 5FU pharmacokinetics of 4 weeks pretreatment with cimetidine, but lack of effect after only 1 week pretreatment remains unexplained.

Whilst no increased toxicity was noted from the higher 5FU concentrations achieved, detailed assessment was not undertaken and further studies will be required to determine whether the higher concentrations are associated with an improved therapeutic ratio. Attention should also be paid to possible increased toxicity of patients receiving concomitant 5FU and cimetidine.

Further studies are indicated to compare the effect of pretreatment with cimetidine and ranitidine, a more potent $H_2$-receptor antagonist which has an unknown effect on cytoplasmic enzymes, but binds less avidly to microsomal enzymes, while the effect on hepatic blood flow is similar to cimetidine (Spahn *et al.*, 1983).

In conclusion, pretreatment of patients with cimetidine for 4 weeks (but not for 1 week or less) led to improved plasma concentrations and AUC following both i.v. and oral 5FU. It seems probable that these alterations to the pharmacokinetics of 5FU were due to a combination of hepatic cytoplasmic enzyme inhibition and reduced hepatic blood flow. Improved absorption following increased gastric and duodenal pH seems unlikely. These observations may have therapeutic implications and in particular indicate that special care should be taken in patients taking these two common drugs concomitantly.

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