Effect of Food on the Oral Bioavailability of UFT and Leucovorin in Cancer Patients

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ABSTRACT

UFT is composed of tegafur (FT), a prodrug of 5-fluorouracil (5-FU), and uracil in a fixed combination (1:4). In conjunction with leucovorin, UFT is being developed for the first-line oral treatment of metastatic colorectal cancer. The effect of food on the oral bioavailability of UFT (2 × 100 mg capsules; dose in terms of FT) and leucovorin (2 × 15 mg tablets) was evaluated in a single-dose, randomized, two-way crossover study. Patients (n = 25) were assigned to receive both drugs after an overnight fast or 5 min after completion of a high-fat meal (721 calories) with a 3-day washout period between treatments; then they were permitted to continue oral UFT/leucovorin therapy for safety assessment. UFT (300 mg/m2/day as three divided doses) and leucovorin (90 mg/day as three divided doses) were given for 28 days. After a 7-day rest, the 28-day cycle was repeated. Pharmacokinetics (n = 22 patients) were determined for FT, 5-FU, uracil, leucovorin, and 5-methyltetrahydrofolate (an active metabolite of leucovorin). The absence of food-effect on peak plasma concentration (Cmax) and the area under the curve (AUC) was concluded if the 90% confidence interval for the ratio of the treatment means was entirely contained in 0.75–1.33. Administration of UFT with food resulted in a 34% decrease in Cmax of FT, whereas the AUC of FT remained unchanged. Food decreased the Cmax and AUC values of uracil and 5-FU by 37–76%. On the contrary, the Cmax and AUC values of leucovorin and 5-methyltetrahydrofolate were increased by 14–60% with food. Time to reach Cmax for all analytes was significantly (P ≤ 0.001) delayed by food. Except for the AUCs of FT, the statistical criterion for concluding a lack of food-effect was not met. These data suggest that UFT/leucovorin should not be dosed simultaneously with food. It is recommended that food should not be consumed for 1 h before and after an oral dose of UFT and leucovorin in a manner similar to pivotal Phase III trials. The 28-day oral regimen of UFT and leucovorin was generally well tolerated in the population studied.

INTRODUCTION

UFT is composed of a fixed molar ratio of FT3 and uracil (1:4). FT is a prodrug of 5-FU, an anticancer agent extensively prescribed for the treatment of colorectal cancer (1). Uracil is a competitive and reversible inhibitor of DPD, which is the rate-limiting enzyme responsible for the catabolism of 5-FU (2). In preclinical studies, coadministration of uracil and FT resulted in an increase in systemic exposure to 5-FU and enhanced antitumor activity compared with that achieved with the administration of FT alone (3, 4). As coadministration of 5-FU with leucovorin has been shown to have clinical benefit (5), UFT plus leucovorin is under development as an oral therapy for the treatment of gastrointestinal malignancies. In pivotal Phase III clinical studies, UFT is administered p.o. at a dose of 300 mg/m²/day, given as three equally divided doses, for 28 days, followed by a 7-day off-treatment period; 30 mg of leucovorin (90 mg/day) is administered concurrently with each dose of UFT. Because the administration of UFT plus leucovorin involves prolonged out-patient therapy, the influence of food on the oral bioavailability of UFT and leucovorin is an important consideration in therapy. Furthermore, although leucovorin has been marketed for several years, the effect of food on the absorption of p.o.-administered leucovorin has not been reported. The presence of food can alter gastric pH, gastric emptying, gastrointestinal motility, and bile excretion, all of which can influence the absorption of p.o.-administered drugs (6). In addition, the bioavailability of p.o.-administered drugs can be influenced by food-drug interactions and changes in drug absorption or metabolism by specific food constituents (7). In the absence of data regarding the influence of food on the oral absorption of both UFT and leucovorin, these drugs have been administered in pivotal clinical studies at least 1 h before or after meals (8). Therefore, the primary objective of this study was to

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3 The abbreviations used are: FT, tegafur; 5-FU, 5-fluorouracil; AUC, area under the concentration-time curve; DPD, dihydropyrimidine dehydrogenase; 5-MTHF, 5-methyltetrahydrofolate; R², coefficient of determination; SD, standard deviation; CI, confidence interval; HPLC, high-performance liquid chromatography.
examine the effect of the administration of a high-fat meal on the single dose oral pharmacokinetics of UFT and leucovorin in cancer patients. In addition, the safety and efficacy of the 28-day regimen of UFT and leucovorin was also examined.

MATERIALS AND METHODS

Patient Selection

Patients with histologically confirmed and measurable advanced solid malignancy that was refractory to standard therapy or for whom no effective therapy existed were candidates for this study. Other eligibility criteria included: (a) age ≥18 years; (b) Eastern Cooperative Oncology Group performance status of ≤2; (c) no chemotherapeutic or radiation therapy in the previous 3 weeks (6 weeks for mitomycin C or nitrosoureas); (d) adequate hematological (absolute neutrophil count ≥1000/µl and platelet count ≥100,000/µl), hepatic (bilirubin ≤1.5 mg/dl), and renal (creatinine ≤1.5 mg/dl) function; and (e) negative pregnancy test and effective means of contraception. Patients with a serious concurrent medical disorder, a history of gastrectomy or malabsorption, major surgery in the previous 3 weeks, and nursing mothers were excluded. While participating on this protocol, patients were not permitted to receive other antineoplastic therapy. Other therapies directed toward patient comfort were allowed, except prophylactic use of antiarrheal drugs. The protocol was approved by the Institutional Review Boards of the University of Arizona Cancer Center, Ottawa Regional Cancer Center, and the M. D. Anderson Cancer Center. Written informed consent was obtained from all patients before the start of the study.

Treatment Plan

Food-Effect Component. A single-dose, two-period, two-treatment, balanced, crossover design was used to evaluate the effect of food. Patients were randomly assigned to receive UFT plus leucovorin after an overnight fast (Fasted) or 5 min after completion of a high-fat meal (Fed). The patients were crossed over after a washout period of 3 days. The fasted patients were given a regular breakfast 2 h after drug administration. For each treatment, UFT was administered p.o. at a fixed dose of 200 mg [2 × 100 mg capsules (dose represented in terms of FT)] and leucovorin was given p.o. at a dose of 30 mg (2 × 15 mg tablets). The study drugs were administered with 5 ounces of room temperature tap water. Patients were allowed to drink water as required during the predose and postdose fasting periods.

The high-fat meal given in this study consisted of two scrambled eggs, two slices of toasted white bread, one teaspoonful of butter, one tablespoonful of jelly, two strips of bacon, 4 oz of hash brown potatoes, and 8 oz of whole milk. The total caloric content of this meal was about 721 calories with 47, 37, and 16% of the calories being obtained from fat (37 g), carbohydrates (67 g), and protein (29 g), respectively. The composition of the meal was similar to that suggested in the draft guidance document by the United States Food and Drug Administration (9). The meal was consumed over a period of 30 min. Portions of the meal were not consumed as documented.

UFT/Leucovorin Therapy. After completion of the food-effect study, patients were allowed to begin therapy with UFT and leucovorin on an outpatient basis. Patients were administered UFT and leucovorin in 35-day treatment cycles comprising 28 days of therapy followed by a 7-day off-treatment period. UFT was given p.o. at a dose of 300 mg/m²/day, equivalent to the dose used in pivotal Phase III trials in patients with metastatic colorectal cancer (8). Body surface area was determined by using the patients’ actual height and weight; if the calculated body surface area was ≥2.2 m², a value of 2.2 m² was used. The total daily dose of UFT was divided into three doses given every 8 h (approximately at 7:00 a.m., 3:00 p.m., and 11:00 p.m.). With each dose of UFT, 30 mg of leucovorin (2 × 15 mg tablets) was administered p.o.; the total daily dose of leucovorin was 90 mg. Patients were asked to take UFT and leucovorin at least 1 h before or after meals, which was similar to drug administration in pivotal Phase III trials. The National Cancer Institute’s Common Toxicity Criteria were used to assess toxicity (10). Dose reduction and/or delays were allowed during a treatment cycle or between treatment cycles as described previously (11). The disease status of each patient was evaluated after every second cycle using the standard criteria for response. Safety was assessed for all patients continuously throughout the study.

Blood Sampling

Two blood samples (3 and 5 ml) were collected after the Fasted and Fed treatments at predose and at 15 and 30 min, and 1, 1.5, 2, 3, 5, 8, and 24 h postdose. Blood samples were collected in potassium EDTA tubes and kept in chipped ice. The tubes used for collecting the 5-ml blood samples contained 5 mg of ascorbic acid powder, which served as an antioxidant for
Within 1 h of collection, blood samples were centrifuged at 5°C at 1000 × g for 15 min and the resulting plasma was stored at or below −20°C until analyses. The first sample (3 ml) was used for the determination of 5-FU and uracil and the second sample (5 ml) for FT, leucovorin, and 5-MTHF.

Sample Analyses

Concentrations of FT were determined by a validated HPLC assay with UV detection based on a method published previously (12), with a minor modification in the mobile phase [methylene chloride-hexane-ethanol (80:20:1.2) was used instead of ethylene chloride-ethanol (24:1)]. A validated gas chromatographic-mass spectrometric assay method was used to quantitate 5-FU and uracil in human plasma samples. The assay method was based on a method published previously for 5-FU (13) and was modified to include the simultaneous quantitation of uracil as reported by Maranuka et al. (12). Before analysis, interference from FT was eliminated by passing the samples through two 200-mg C18 solid-phase extraction columns. Leucovorin and 5-MTHF were determined by validated HPLC methods that were modifications of methods reported previously (14, 15). Leucovorin and 5-MTHF were extracted from plasma as described by Etienne et al. (14); however, leucovorin was resolved from endogenous interference using a gradient HPLC [mobile phase A, 40% acetonitrile-50% methanol in 25 mM KH$_2$PO$_4$ (pH 2.3); mobile phase B, 25 mM KH$_2$PO$_4$ (pH 2.3)], and 5-MTHF was resolved from endogenous interference by isocratic HPLC using a mobile phase consisting of 5% acetonitrile-5% methanol in 25 mM KH$_2$PO$_4$ (pH 2.3). Both leucovorin and 5-MTHF were detected at 310 nm (15).

For FT, 5-FU, and uracil, the standard curves were linear [($R^2$) ≥0.989] over the concentration range of 50–20,000, 1–500, and 20–5,000 ng/ml, respectively. On the basis of the analyses of quality control samples (at three concentrations analyzed in triplicate in each analytical run), the accuracy of the assays for FT, 5-FU, and uracil was >94%, and the inter- and intra-run precision was >85%. For both leucovorin and 5-MTHF, the standard curves were linear [($R^2$) ≥0.984] over the concentration range of 50–2,000 ng/ml; the accuracy of the assay methods was >88%, and the inter- and intra-run precision was >86%.

Pharmacokinetic Analyses

The plasma concentration-time data following administration of the Fasted and Fed treatments for all 5 analytes were analyzed by a noncompartmental method (16). The peak plasma concentration, CMAX, and the time to reach peak concentration, TMAX, were recorded directly from experimental observations. The area under the plasma concentration-time curve from time 0 to T, AUC(0-T), where T is the time of last measurable concentration, was calculated by the trapezoidal method. Using no weighting factor, the slope of the terminal phase of the plasma profile, K, was determined by log-linear regression of at least three data points, which yielded a minimum mean square error. The absolute value of K was used to estimate the terminal half-life (T-HALF) by the formula T-HALF = ln2/K. The area under the plasma concentration-time curve from 0 to infinity, AUC(INF), was determined by summing the areas from time 0 to the time of last measured concentration, calculated by using conventional trapezoidal and log-trapezoidal methods, and the extrapolated area. The extrapolated area was determined by dividing the final concentration by the slope of the terminal log-linear phase.

Statistics

To evaluate the effect of food on the pharmacokinetics of UFT and leucovorin, an ANOVA for a two-way cross-over design was performed on mean CMAX and AUC(0-T) values for all five analytes. [AUC(INF) values were not used for statistical analyses because this parameter could not be determined in several subjects]. Factors in the analysis were sequence, patient within sequence, period, and treatment. Patients, nested within sequence, were considered as random terms and the sequence effects were tested using patient (within sequence) mean square from the ANOVA, as the error term. Ninety-percent confidence limits for the differences between the least squares means on the natural log scale were converted to confidence limits for the ratio on the original scale. Absence of effect of food on CMAX and AUC(0-T) was concluded if the 90% CI for the ratio of the treatment means was entirely contained between 0.75 to 1.33. The interval of 0.75–1.33 was established a priori based on the reported variability in the pharmacokinetic parameters for FT, uracil, and leucovorin (17). For the CMAX and AUC(0-T) values for uracil, 22 patients...
Food-Effect Study of UFT and Leucovorin

Therefore, AUC(0-T) values were used for evaluating confidence in estimating half-lives and AUC(INF) values. Provided 80% power to conclude that the ratio of the treatment means was contained in 0.75–1.33. For the CMAX and AUC(0-T) values for FT, this sample size provided >90% power to conclude that the ratio of the treatment means was contained in 0.75–1.33, and >80% power for the ratio of treatment means for leucovorin CMAX and AUC(0-T) values. TMAX was analyzed using Koch’s procedure (18). All statistical analyses were carried out using SAS/STAT, Version 6.08 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics. A total of 25 patients were enrolled into the study. The majority of patients (44%) had either colon or metastatic colon cancer as their primary diagnosis. The patients (15 males and 10 females) had a median (range) age of 64 (26–81) years. The demographic characteristics of the patients are summarized in Table 1. Only 22 of 25 patients were evaluable for pharmacokinetics (3 patients were unable to complete both treatments of the study), but all 25 patients were evaluable for safety.

Meal Consumption. Sixteen of 22 cancer patients evaluable for pharmacokinetics were able to complete the entire meal prescribed for the food-effect component of the study. In the six patients who could not complete the meal, the median (minimum, maximum) caloric consumption was 570 (467, 721) kcal. Overall, for the 22 evaluable patients, the median (minimum, maximum) caloric consumption was 721 (467, 721) kcal. Per the protocol, majority of the patients (16 of 22) consumed UFT plus leucovorin within 5 min after completion of meal; 3, 1, and 2 patients were dosed within 10, 15, and 20 min, respectively.

Pharmacokinetic Analyses. The mean plasma concentration-time profiles for UFT and leucovorin analytes are presented in Fig. 1 and 2, respectively, and the mean (SD) pharmacokinetic parameters are presented in Tables 2 and 3, respectively. A clear terminal log-linear phase could not be identified in 2 to 15 patients for 5-FU, uracil, leucovorin, and 5-MTHF after Fed and Fasted treatments, resulting in lack of confidence in estimating half-lives and AUC(INF) values. Therefore, AUC(0-T) values were used for evaluating differences between treatments.

FT was rapidly absorbed after oral administration of UFT under fasting conditions, and peak concentrations were reached by 1.0 h (Fig. 1). When administered with meals, the mean CMAX value of FT decreased by 34%, whereas the TMAX was significantly delayed with food (Table 2). AUC(0-T) values of FT were comparable between treatments (Table 2). After CMAX, the plasma FT levels declined in a monoexponential manner with a mean T-HALF of 8.3 and 7.5 h for the Fasted and Fed treatments, respectively.

In case of 5-FU, the CMAX and the AUC(0-T) values were reduced by 70% and 37%, respectively, when UFT was taken with food is quite marked and may impact its antitumor efficacy.

Uracil was also rapidly absorbed after administration of UFT on an empty stomach (TMAX = 1 h; Fig. 1). Administration of UFT with meal markedly reduced the CMAX and AUC(0-T) for uracil by 76% and 66%, respectively, compared with dosing on an empty stomach (Table 2). Moreover, TMAX was significantly delayed with food (P = 0.001). Under fasting condition, the T-HALF of uracil was 0.88 h. For the Fed

### Table 2  Mean (SD) pharmacokinetic parameters for UFT-related analytes (FT, 5-FU, and uracil)

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Fasted</th>
<th>Fed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetic parameters for FT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMAX (ng/ml)</td>
<td>6623 (1598)</td>
<td>4391 (960)</td>
</tr>
<tr>
<td>TMAX (h)</td>
<td>1.0 (0.5, 2.0)</td>
<td>3.0 (1.5, 5.0)</td>
</tr>
<tr>
<td>AUC(0-T) (brng/ml)</td>
<td>51338 (16202)</td>
<td>50138 (13840)</td>
</tr>
<tr>
<td>T-HALF (h)</td>
<td>8.3 (2.8)</td>
<td>7.5 (1.5)</td>
</tr>
<tr>
<td>AUC(INF) (brng/ml)</td>
<td>57622 (20092)</td>
<td>53637 (18229)</td>
</tr>
<tr>
<td><strong>Pharmacokinetic parameters for 5-FU</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMAX (ng/ml)</td>
<td>115 (116)</td>
<td>34 (42)</td>
</tr>
<tr>
<td>TMAX (h)</td>
<td>0.5 (0.25, 2.0)</td>
<td>2.0 (0.5, 5.0)</td>
</tr>
<tr>
<td>AUC(0-T) (brng/ml)</td>
<td>118 (95)</td>
<td>74 (85)</td>
</tr>
<tr>
<td>T-HALF (h)</td>
<td>3.4 (2.0)</td>
<td>3.2 (2.1)</td>
</tr>
<tr>
<td>AUC(INF) (brng/ml)</td>
<td>126 (96)</td>
<td>82 (79)</td>
</tr>
<tr>
<td><strong>Pharmacokinetic parameters for uracil</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMAX (ng/ml)</td>
<td>2823 (2647)</td>
<td>682 (757)</td>
</tr>
<tr>
<td>TMAX (h)</td>
<td>1.0 (0.25, 2.0)</td>
<td>2.0 (0.5, 5.0)</td>
</tr>
<tr>
<td>AUC(0-T) (brng/ml)</td>
<td>118 (95)</td>
<td>74 (85)</td>
</tr>
<tr>
<td>T-HALF (h)</td>
<td>3.4 (2.0)</td>
<td>3.2 (2.1)</td>
</tr>
<tr>
<td>AUC(INF) (brng/ml)</td>
<td>126 (96)</td>
<td>82 (79)</td>
</tr>
</tbody>
</table>

* a n = 19–22; a terminal log-linear phase could not be identified in three patients.
* b Median (minimum, maximum) value.
* c T ranged from 8–24 h, 3–24 h, and 1.5–8 h for FT, 5-FU, and uracil, respectively.
* d ND, not determined. A terminal log-linear phase was not identified in a majority of the patients.
treatment, a terminal log-linear phase could not be determined in a majority of the patients (15 of 22), and hence the half-life was not determined.

For leucovorin, the CMAX and AUC(0-T) values increased by 31% and 60%, respectively, when given with food compared with administration on an empty stomach (Table 3 and Fig. 2). A similar trend was seen for 5-MTHF, where the CMAX and AUC(0-T) values were higher by 14% and 46%, respectively, when leucovorin was given with food (Table 3 and Fig. 2). The TMAX values for both leucovorin and 5-MTHF were significantly (P = 0.001) delayed by food. Half-lives were reasonably comparable across treatments for both the analytes.

Statistical Analyses. The point estimates for the ratio of the mean CMAX and AUC(0-T) values for the Fed versus Fasted treatments and the 90% CIs are provided in Table 4. Except for the AUC(0-T) values for FT, the 90% CIs for the ratio of mean CMAX and AUC(0-T) values for all analytes were not entirely contained within 0.75–1.33, suggesting a failure to conclude lack of food-effect. The 90% CI for AUC(0-T) of FT was entirely contained within the interval of 0.75–1.33, indicating that there was no food effect for the AUC parameter for FT.

Toxicity and Efficacy Results. UFT administered on the 28-day regimen was generally well tolerated. However, of the 25 patients enrolled in the study, 24 experienced at least one adverse event. A total of 205 adverse events were reported, of which 87% were less than or equal to grade 2. The most frequent adverse events were summated in Table 5. Eighteen grade 3 events (9%) were reported, but only 3 of them (rash, 1; weakness, 1; and diarrhea, 1) were assessed as being related to the study medication. The single grade 4 event was congestive heart failure and was assessed to be unrelated to the study drug. Nine patients experienced severe adverse events, but only one (asthenia in one patient) was assessed to be related to the study medications. There were 13 deaths among the patients enrolled in the study; all were related to the effects of the underlying malignant disease.

There were no partial or complete responses achieved in this study. A majority of patients (64%; 16 of 25) had progressive disease on the study. Five patients (20%) maintained stable disease for a median (range) of four courses (2–10 courses). The response for the remaining four patients was assessed as “not determinable.”

### DISCUSSION

The primary objective of this study was to evaluate the effect of food on the oral pharmacokinetics of UFT and leucovorin. The most notable observation of the study was that administration of UFT with food may decrease the systemic exposure to 5-FU, the active cytotoxic moiety of UFT, which may result in reduced antitumor activity. Hence, UFT should not be given simultaneously with food. Other key differences between the Fed and Fasted treatments were a decrease in the rate of FT absorption, reduced exposure to uracil, and increased exposure to leucovorin and 5-MTHF.

FT is a prodrug of 5-FU, and the proposed pathways for the conversion are the oxidation by microsomal enzymes and hydrolysis by the cytosolic enzymes with the liver being a predominant organ involved in the metabolism of FT (19, 20). Once formed from FT, plasma 5-FU levels are mainly determined by DPD-mediated catabolism of 5-FU leading to higher breakdown of 5-FU. Leucovorin or 5-MTHF are structurally diverse and their metabolism pathways are different from 5-FU. Hence it appears that leucovorin/5-MTHF or changes in their metabolism may offer less inhibition of DPD-mediated catabolism of 5-FU leading to higher breakdown of 5-FU. Leucovorin or 5-MTHF are structurally diverse and their metabolism pathways are different from 5-FU. Hence it appears that leucovorin/5-MTHF or changes in their kinetics are unlikely to interfere with the disposition of 5-FU.

### Table 3 Mean (SD) pharmacokinetic parameters for leucovorin-related analytes (leucovorin and 5-MTHF)

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Fasted</th>
<th>Fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMAX (ng/ml)</td>
<td>346 (252)</td>
<td>453 (254)</td>
</tr>
<tr>
<td>TMAX (h)</td>
<td>2.5 (1.5, 5.0)</td>
<td>3.0 (2.0, 8.0)</td>
</tr>
<tr>
<td>AUC(0-T) (hng/ml)</td>
<td>3131 (2841)</td>
<td>5039 (4110)</td>
</tr>
<tr>
<td>T-HALF (h)</td>
<td>15.4 (13.4)</td>
<td>9.8 (4.1)</td>
</tr>
<tr>
<td>AUC(INF) (hng/ml)</td>
<td>5552 (2983)</td>
<td>7372 (5723)</td>
</tr>
</tbody>
</table>

* Because of insufficient plasma samples for reanalysis and because a terminal log-linear phase could not be identified in several patients, n = 14–22.

* Median (minimum, maximum) value.

* T ranged from 1.5–24 h and 3–24 h for leucovorin and 5-MTHF, respectively.

### Table 4 Point estimate and 90% CI for the ratio of geometric mean CMAX and AUC(0-T) values for all analytes

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Pharmacokinetic parameter</th>
<th>Ratio of means (Fed:Fasted)</th>
<th>Point estimate</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT</td>
<td>CMAX</td>
<td>0.667</td>
<td>(0.609–0.731)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC(0-T)</td>
<td>0.985</td>
<td>(0.918–1.056)</td>
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</tr>
<tr>
<td></td>
<td>Uracil</td>
<td>0.283</td>
<td>(0.162–0.496)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC(0-T)</td>
<td>0.387</td>
<td>(0.249–0.603)</td>
<td></td>
</tr>
<tr>
<td>5-FU</td>
<td>CMAX</td>
<td>0.345</td>
<td>(0.214–0.557)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC(0-T)</td>
<td>0.678</td>
<td>(0.508–0.904)</td>
<td></td>
</tr>
<tr>
<td>Leucovorin</td>
<td>CMAX</td>
<td>1.531</td>
<td>(1.239–1.893)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC(0-T)</td>
<td>2.109</td>
<td>(1.260–3.530)</td>
<td></td>
</tr>
<tr>
<td>5-MTHF</td>
<td>CMAX</td>
<td>1.199</td>
<td>(1.050–1.368)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC(0-T)</td>
<td>1.911</td>
<td>(1.353–2.700)</td>
<td></td>
</tr>
</tbody>
</table>

* Units for CMAX and AUC(0-T) are ng/ml and hng/ml, respectively.

* Both parameters were analyzed on a log scale. Point estimates are based on geometric means.
The composition of the meal was similar to that suggested in the draft guidance document by the United States Food and Drug Administration (9). The meal may seem substantial for cancer patients who are terminally ill. But a majority of these patients (16 of 22) completed the entire meal, and the remaining 6 patients consumed at least 65%; hence the meal was considered adequate for evaluating food-effect. The data were not statistically analyzed for food-effect upon excluding the six subjects who did not complete the meal because of lack of adequate statistical power after reducing the sample size. Comparison of pharmacokinetic parameters in the six subjects with incomplete meals was suggestive of a food-effect on the oral absorption of UFT and leucovorin in a manner similar to that stated above. Per the draft guidance, issued after initiation of this study, absence of food-effect could be concluded if the 90% CI for the ratio of the means for Fed and Fasted treatments fall entirely within 0.7–1.43 and 0.8–1.25 for CMAX and AUC, respectively. Furthermore, a food-effect can be documented if the CI values fall entirely outside the intervals specified above, and that food-effect was indeterminate if the above two criteria are not met (9). Considering these guidelines, only the 90% CI values for the ratio of the mean CMAX of 5-MTHF and AUC of FT were within the specified range. This indicates that simultaneous administration of UFT with a high-fat meal will reduce the systemic exposure to the active cytotoxic moiety of UFT (5-FU).

UFT and leucovorin were generally well tolerated when administered on the 28-day oral regimen. Most of the adverse events after administration of UFT were related to gastrointestinal tract (nausea and diarrhea) which is consistent with the side effect profile observed after i.v. 5-FU administration (27).

In summary, the data obtained from this study suggest that simultaneous administration of UFT with food will reduce the systemic exposure to 5-FU which may compromise the antitumor activity of UFT. Hence, UFT plus leucovorin should not be taken simultaneously with food. At the present, it is recommended that food should not be consumed for at least 1 h before and after an oral dose of UFT and leucovorin because this was the procedure used in pivotal Phase III clinical trials that have demonstrated that the combination of UFT plus leucovorin is as effective and significantly safer when compared with i.v. 5-FU and leucovorin (8).

### References


Effect of Food on the Oral Bioavailability of UFT and Leucovorin in Cancer Patients

Bharat Damle, Farhad Ravandi, Sanjeev Kaul, et al.


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