Effect of Food on the Pharmacokinetics of Capecitabine and Its Metabolites following Oral Administration in Cancer Patients

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ABSTRACT

Capecitabine (Ro 09-1978) is a novel oral fluoropyrimidine carbamate that was rationally designed to generate 5-fluorouracil (5-FU) selectively in tumors. The effect of food on the pharmacokinetics of capecitabine and its metabolites was investigated in 11 patients with advanced colorectal cancer using a two-way cross-over design with randomized sequence. Patients received repeated doses of 666 or 1255 mg/m² of capecitabine twice daily. On study days 1 and 8, drug was administered following an overnight fast or within 30 min after consumption of a standard breakfast, and serial blood samples were collected. Concentrations of capecitabine and its metabolites [5'-deoxy-5-fluorouridine (5'-DFCR), 5'-deoxy-5-fluorouridine (5'-DFUR), 5-FU, dihydro-5-fluorouracil (FUH₂), and α-fluoro-β-alanine (FBAL)] in plasma were determined by high-performance liquid chromatography or liquid chromatography/mass spectroscopy. Intake of food prior to the administration of capecitabine resulted in pharmacokinetic changes of all compounds involved. The extent of these changes, however, varied considerably between the various compounds. Maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) values were decreased after food, and time until the occurrence of Cmax values were increased. In contrast, the apparent elimination half-life was not affected by food intake. The extent of change in Cmax and AUC was highest for capecitabine and decreased with the order of formation of the metabolites. The “before:after food” ratios of the Cmax values were 2.47 for capecitabine, 1.81 for 5'-DFCR, 1.53 for 5'-DFUR, 1.58 for 5-FU, 1.26 for FUH₂, and 1.11 for FBAL. The before:after food ratios of the AUC values were 1.51 for capecitabine, 1.26 for 5'-DFCR, 1.15 for 5'-DFUR, 1.13 for 5-FU, 1.07 for FUH₂, and 1.04 for FBAL. The results show that food has a profound effect on the AUC of capecitabine, a moderate effect on the AUC of 5'-DFCR, and only a minor influence on the AUC of the other metabolites in plasma. In addition, a profound influence on Cmax of capecitabine and most of its metabolites was found. Detailed information on the relationship between concentration and safety/efficacy is necessary to evaluate the clinical significance of these pharmacokinetic findings. At present, it is recommended that capecitabine be administered with food as this procedure was used in the clinical trials.

INTRODUCTION

Fluorinated pyrimidines, including 5-FU2 and 5-fluorouracil, play a major role in the treatment for many common tumors (1). Their major use is in combination with other cytostatics or modulators. 5-FU, frequently used in combination with leucovorin, is the standard for adjuvant treatment of surgically resected colorectal cancer (2, 3). 5-FU given as protracted i.v. infusion to breast and colorectal cancer patients is proposed as a technique for improving the activity of this drug. However, this approach requires a surgically placed permanent i.v. access with the consequence of catheter-related complications. An oral route of administration ideally circumvents these problems. Thus, fluorinated pyrimidines that can be administered p.o. are being developed.

Capecitabine (Xeloda) is a novel fluoropyrimidine carbamate that was rationally designed as a p.o.-administered, tumor-activated, and tumor-selective cytotoxic agent (Fig. 1). After oral administration, capecitabine passes through the intestinal mucosa as an intact molecule and is first metabolized in the liver to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumor. Further catalytic activation of 5'-DFUR to 5-FU then occurs at the tumor site by the tumor-associated angiogenic factor thymidine phosphorylase, thereby minimizing the exposure of healthy body tissues to 5-FU. After administration of capecitabine to colorectal cancer patients, 5-FU concentrations in the primary...
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...tumor were found to be approximately 3 times greater than in adjacent healthy tissue and 14 times greater than in plasma (4). As described previously in the literature, 5-FU is further catabolized to FUH₂, 5-fluoro-ureido-propionic acid, and FBAL (5).

The pharmacokinetics of capecitabine and its metabolites have been investigated in several Phase I studies. Capecitabine is well absorbed after oral administration and is then extensively converted to the main metabolite, 5'-DFUR. The peak of concentration for intact drug and 5'-DFUR occurs after 2 h (median value), and then concentrations decline rapidly with a half-life of less than 1 h (6–8). Capecitabine is a systemic precursor of 5'-DFCR (doxifluridine). p.o.-administered doxifluridine has been licensed in Japan, Korea, and China for use in breast, colorectal, and gastric cancer. The limitation of doxifluridine comes from its gastrointestinal toxicity, particularly diarrhea (9). These adverse-effects of doxifluridine are attributed to the release of 5-FU within the small intestine, where thymidine phosphorylase is also present. The pharmacology of doxifluridine has been extensively investigated both in animals (10, 11) and in cancer patients (9, 12). A review article (13) provides an excellent overview of the literature on doxifluridine.

The objective of this study was to investigate the effect of food on the pharmacokinetics of capecitabine and its metabolites in cancer patients. In vitro studies revealed that capecitabine is unstable under strongly acidic conditions.3 Degradation of capecitabine in an empty stomach at low pH might result in a decrease of the amount of unchanged drug being available for absorption. In clinical studies, capecitabine was always administered after food intake because it is well established that the presence of food increases the pH in the stomach. As a secondary objective, the present pharmacokinetic study was designed to provide information on the potential degradation of capecitabine in vivo when administered in fasted conditions.

MATERIALS AND METHODS

Substance. Capecitabine was synthesized at F. Hoffmann-La Roche, Basel, according to the rules of Good Manufacturing Practice. For clinical use, film-coated tablets containing 150 and 500 mg of capecitabine were produced.

Patients. Eleven subjects from the patients’ pool of an efficacy and safety study investigating different dose regimens of capecitabine agreed to participate in this pharmacokinetic evaluation. These 11 patients had histologically or cytologically confirmed advanced and/or metastatic measurable colorectal adenocarcinoma and had not previously received chemotherapy. They were hospitalized at the oncology departments of four different centers: Royal Infirmary in Aberdeen, United Kingdom; Western Infirmary in Glasgow, United Kingdom; Universitair Ziekenhuis in Antwerpen, Belgium; and Dr. Daniel den Hoed Kliniek in Rotterdam, Belgium. The patients (two females and nine males) were 53–80 years of age (mean, 65.9 years), weighed 49–107 kg (mean, 77.4 kg), and their body surface was 1.54–2.29 m² (mean, 1.91 m²); their Karnofsky performance status was 70–100% (median, 100%).

Study Design. This was an open label, multicenter, randomized efficacy, safety, and pharmacokinetic study in 109 colorectal cancer patients (14). The study was conducted in full agreement with the principles of the Declaration of Helsinki III (as amended in Tokyo, Venice, and Hong Kong), and the trial protocol was approved prior to study start by the local Ethical Review Boards. Written informed consent was obtained from each patient before study start. Screening before start of the trial included, in addition to the usual recordings and measurements, tumor assessments and evaluation of the Karnofsky performance status. During treatment, vital signs, physical examination, hematology, blood chemistry, urinalysis, electrocardiogram, monitoring of adverse events, and tumor assessments were performed.

Carefully selected inclusion/exclusion criteria taking into account the stage of the disease, the current medical status, and life expectancy of the patients were applied to obtain evaluable clinical and pharmacokinetic data.

Patients received 666 mg capcitabine/m² twice daily as continuous therapy or 1255 mg/m² twice daily as intermittent treatment (2 weeks treatment followed by 1 week rest). The treatment was at least 6 weeks. Eleven patients were selected for the pharmacokinetic part of the study. 6 receiving the continuous treatment and 5 the intermittent treatment according to a randomized two-way cross-over with respect to capcitabine being taken fasted or after breakfast on study days 1 and 8. Capecitabine was administered p.o. 30 min after food intake in the morning or on an empty stomach after an overnight fast. The fasted patients received a regular breakfast ≥2 h after the morning drug intake.

Food. The standard breakfast at each center was administered. The consumed breakfasts were judged as medium rich in fat and carbohydrates and consisted of a small selection of the following items: porridge, tea, milk, coffee, orange juice, bread, butter, marmalade, cheese, ham, cereals, fruit, and yogurt.

Blood Sampling. Blood samples of 5 ml were taken at 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, and 8 h after drug administration on study days 1 and 8, using vacutainers containing EDTA as

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anticoagulant. Blood samples were centrifuged, and the supernatant plasma was removed and stored in plastic tubes at −20°C until analysis.

**Drug Assay.** Capecitabine and its five metabolites were extracted from plasma samples following the addition of internal standards (Ro 09-1977, tegafur, [15N2]-5-FU, [13C, 15N2]-FUH2, and β-Ala-Ala) and precipitation with acetonitrile. The compounds in the supernatant were separated into two fractions using an automatic solid phase extraction system (Bond Elut column C18 Varian); capecitabine, 5'-DFCR, and 5'-DFUR were eluted with methanol (fraction A); and 5-FU, 5-FUH2, and FBAL were eluted with ammonium acetate (fraction B).

Capecitabine, 5'-DFCR, and 5'-DFUR from fraction A were separately analyzed by reversed-phase high-performance liquid chromatography. For determination of capecitabine, a YMC-Pack C8-AM column (150 × 6.0-mm inside diameter, 5 μm; YMC Co., Ltd., Kyoto, Japan) was used; the mobile phase consisted of acetonitrile/citrate buffer [50 ml of Titrisol (pH 4.0, Merck) diluted to 1200 ml with water] (40:60, v/v), and the flow rate was 1.0 ml/min. UV detection was at 260 nm. The retention times of capecitabine and of Ro 09-1977 (internal standard) were approximately 6.2 and 8.8 min, respectively. 5'-DFCR and 5'-DFUR were analyzed simultaneously by high-performance liquid chromatography using a Supersphere ODS column (250 × 4.6-mm inside diameter, 5 μm; Shiseido Co., Ltd., Tokyo, Japan); the mobile phase consisted of acetonitrile/methanol/citrate buffer and 50 ml of Titrisol (pH 4.0) diluted to 1740 ml with water (3:10:87, v/v), and the flow rate was 0.8 ml/min. UV detection was at 267 nm. The retention times of 5'-DFCR, 5'-DFUR, and tegafur (internal standard) were approximately 10.3, 14.3, and 19.0 min, respectively.

The two metabolites 5-FU and 5-FUH2 from fraction B were simultaneously analyzed on a reversed-phase column (J'sphere ODS-M80, 150 × 4.6-mm inside diameter, 4 μm; YMC) with ion-spray MS/MS detection (negative, selected reaction-monitoring ions were m/z 129/42, 131/43, 131/83, and 134/85 for 5-FU, [15N2]-5-FU, 5-FUH2, and [13C, 15N2]-5-FUH2, respectively). The mobile phase consisted of methanol/5 mm ammonium formate (15:85, v/v). The flow rate was 1.0 ml/min. UV detection was at 310 nm. The retention times of 5-FU and C18 were approximately 10.9 and 14.7 min, respectively. For 5-FU, the limit of quantification was 3 ng/ml using a 0.5-ml plasma specimen, and the interassay precision from STD and QA samples (overall CV%) was 3.5% in the calibration range 3–1500 ng/ml; for FBAL, the limit of quantification was 0.02 μg/ml (0.5 ml plasma), and the interassay precision reached 6.3% in the calibration range 0.02–10 μg/ml.

**Pharmacokinetic Parameters.** The pharmacokinetic parameters of capecitabine and its metabolites (5'-DFCR, 5'-DFUR, 5-FU, FUH2, and FBAL) were determined from the concentration-time data on days 1 and 8 and estimated using noncompartmental methods (15).

The following parameters were estimated. Maximum plasma concentrations (Cmax) and time of their occurrence (tmax) were determined from the observed highest concentration and its occurrence, respectively. Apparent elimination half-life (t1/2) was estimated from ln 2/k, where the apparent rate constant of elimination, k, was estimated by linear regression on the logarithm of the plasma concentration versus time data. Area under the plasma concentration-time curve from time 0 to infinity (AUC0-∞) was estimated from the sum of AUC0-t and C1-last/k. AUC0-∞ is the area under the curve from time 0 to the last sampling time (t last) at which the concentration could be measured (C1-last). AUC0-12 was estimated using the linear trapezoidal rule. For FBAL, AUC0-12 had to be calculated and used for statistical comparison.

**Descriptive Statistics.** Descriptive statistics were used to summarize the pharmacokinetic parameters. Geometric mean and geometric CV are reported for Cmax and AUC0-∞. Arithmetic mean and CV for t1/2, and median, minimum, and maximum values for tmax.

**Comparative Statistics.** The primary parameter for the testing of the food effect was the dose-adjusted AUC0-∞ of the analyte 5'-DFUR. The analysis performed was a three-way ANOVA with the factors treatment, subject, and period applied to the log-transformed variables. A two-sided 90% confidence interval for the ratio of the effect of the administration of capecitabine before food relative to the administration of capecitabine after food was calculated from the least squares means of the final model and its covariance matrix. It was concluded that no relevant food effect was found if the 90% confidence limits are included within 70–143%. The selection of this interval was based on the preliminary information available about the therapeutic window at the time the study protocol was written.

For the other pharmacokinetic parameters, dose-adjusted AUC0-∞ and Cmax of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU, FUH2, and FBAL, the same statistical analysis was repeated (three-way ANOVA and 90% confidence intervals) but interpreted in an exploratory sense only.

tmax was tested for food effect using a paired Wilcoxon test for the log-transformed parameters.

All comparisons were made at the level α = 0.05.

**RESULTS**

**Effect of Food.** The pharmacokinetic profiles (arithmetic mean concentration values versus time) obtained after administration of 1255 mg/m2 capecitabine before and after food intake are shown for capecitabine, 5'-DFCR, 5'-DFUR, 5-FU, and
Fig. 2. Plasma concentration of capecitabine (arithmetic mean values) versus time data after administration of capecitabine after and before food intake (dose level of 1255 mg/m²) in colorectal cancer patients.

Fig. 3. Plasma concentration of 5'-DFCR (arithmetic mean values) versus time data after administration of capecitabine after and before food intake (dose level of 1255 mg/m²) in colorectal cancer patients.

FBAL in Figs. 2–6, respectively. For all analytes, higher peak concentrations and shorter $t_{\text{max}}$ values were observed in the fasted patients compared with those who had breakfast before drug intake. An identical observation was made after the lower dose of 666 mg/m² capecitabine. Descriptive statistics on the pharmacokinetic parameters of capecitabine and its metabolites estimated after and before food intake in 11 cancer patients after administration of two dose levels of capecitabine (666 and 1255 mg/m²) are presented in Table 1. $C_{\text{max}}$ and AUC values were normalized to a dose of 1255 mg/m². This normalization is justified because the pharmacokinetics of capecitabine and its metabolites are dose proportional within the dose range studied (6, 16). Comparative statistics on $C_{\text{max}}$, $t_{\text{max}}$, and $AUC_{0-\infty}$ for capecitabine and its metabolites are provided in Table 2. The parameters $C_{\text{max}}$ and $AUC_{0-\infty}$ were dose-normalized and log-transformed; in addition, a Wilcoxon test was performed on the log-transformed $t_{\text{max}}$ values.

Irrespective of the influence of food, the pharmacokinetic parameters of capecitabine and its metabolites showed large differences between analytes (Table 1). Depending on the rate of formation and elimination of the various metabolites, differences up to 20-fold were observed for $C_{\text{max}}$ (5-FU versus...
5'-DFUR) and even up to 40-fold for AUC (5-FU versus FBAL). Less marked differences existed between \( t_{1/2} \) values (up to 3-fold) and \( t_{\text{max}} \) values.

Intake of a standard breakfast prior to the administration of capecitabine resulted in pharmacokinetic changes of the parent drug and its metabolites. The \( C_{\text{max}} \) and AUC values were decreased after food, and \( t_{\text{max}} \) values were increased. These changes, however, varied considerably between the involved compounds. In contrast, \( t_{1/2} \) was not affected by food intake (Table 1).

The "before:after food" ratio of the \( C_{\text{max}} \) and AUC values were highest for capecitabine and decreased with the order of formation of the metabolites (5'-DFCR → 5'-DFUR → 5-FU → FUH₂ → FBAL; Table 2). From a statistical point of view, AUC₀→∞ of 5'-DFUR was defined as the primary pharmacokinetic parameter. Using the acceptance region of 70–143%, as defined a priori, it can be concluded that there is no relevant food effect on the AUC₀→∞ of 5'-DFUR.

For the primary variable AUC₀→∞ of 5'-DFUR, neither the dose effect nor the dose \( \times \) food interaction term were significant \((P \geq 0.28)\).

The before:after food ratio of the median values of \( t_{\text{max}} \) reflected for all compounds a faster appearance in plasma when capecitabine was administered on an empty stomach (Table 2).
This decrease in time to peak was major for 5'-DFCR and 5-FU, intermediate for capcitabine and 5'-DFUR, and less pronounced for FUH₂ and FBAL. All differences were statistically significant based on the performed Wilcoxon test.

**Effect of Time.** The effect of food on the pharmacokinetics of capcitabine and its metabolites was studied on days 1 and 8. The results of the ANOVA showed that there is no time effect on the pharmacokinetics parameters (Cmax and AUC) of capcitabine and its metabolites, with the exception of 5-Hi and FBAL. For the parameters AUC and Cmax of 5-Hi, the factor period had Ps of 0.001 and 0.0127. The time effects were estimated as increases from day 1 to day 8 of 49% (0.593 versus 0.886 µg·h/ml) and 73% (0.289 versus 0.501 µg·h/ml), respectively. For the parameters AUC and Cmax of FBAL, the factor period had Ps of 0.018 and 0.006. The time effects were estimated as increases from day 1 to day 8 by 14% (28.8 versus 32.7 µg·h/ml) and 16% (5.49 versus 6.39 µg·h/ml), respectively. Because the design is a cross-over design and the factor period was included in the analysis, the time effect does not bias the estimation of the food effect.

**Safety/Efficacy.** The safety and efficacy results for each of the schedules (continuous and intermittent treatments) have been published elsewhere (14). Because capcitabine was administered only once without food, no information on safety before food versus after food could be obtained from this study.

**DISCUSSION**

The objective of this study was to investigate the effect of food on the pharmacokinetics of capcitabine and its metabolites in cancer patients. In view of the dose reduction of 25 or 50% recommended in case of adverse effects, the doses used in this study (666 and 1255 mg/m²) to investigate the effect of food cover the therapeutic dose range for capcitabine. The cancer patients were asked to eat a standard breakfast provided by the hospital. Although this breakfast was not of the same content for all patients, the results demonstrate that the study was adequately designed to show an effect of food on the pharmacokinetics of capcitabine and its metabolites.

The results show that food has a profound effect on Cmax of capcitabine, 5'-DFCR, 5'-DFUR, 5-FU, and on AUC0-∞ of capcitabine but only a moderate to minor effect on AUC and Cmax of the other metabolites. In addition, food has an effect on the input rate of all metabolites, as demonstrated by the changes in fmax values (Table 2). The influence of food on Cmax and AUC was highest for capcitabine and decreased for the metabolites in the order of their formation, suggesting a "dilution" of the original effect. Food can influence pharmacokinetics of drugs in many different ways (17). Saturation of the metabolism during hepatic first pass for the first two metabolic steps (intact drug to 5'-DFCR and 5'-DFCR to 5'-DFUR) could explain the results obtained in this study. In fasted conditions, the rate of capcitabine absorption is much faster, which leads to very high concentrations entering into the liver. These very high concentrations in fasted patients would lead to saturable hepatic first pass. Lower clearances of intact drug and 5'-DFCR in fasted conditions would explain the profound increase in AUC of these two compounds. Although clearances are different, the total amount of 5'-DFCR and 5'-DFUR formed is almost the same in fasted and fed conditions because renal clearance contributes very little (urinary excretion for each metabolite, <10%) to the elimination of intact drug and 5'-DFCR (18, 19). If a metabolite is not metabolized during first pass through the liver, it will be metabolized later. This would explain why food has a progressively smaller effect on the AUC of subsequent metabolites (5'-DFUR, 5-FU, FUH₂, and FBAL).

*In vitro* studies investigating the cell-killing effect of 5-FU showed that the efficacy of 5-FU is AUC dependent (20). High drug concentrations of 5-FU are needed if exposure time of tumor cells is short, but low concentrations are effective if the exposure time is long. In general in oncology, efficacy and
within 30 mm after food intake because this was the procedure.

Methods.

Table 2  Estimated ratios before food:after food for \( C_{\text{max}} \), \( t_{\text{max}} \), and \( \text{AUC}_{0-\infty} \)

\( C_{\text{max}} \) and \( \text{AUC}_{0-\infty} \) values were normalized to a dose of 1255 mg/m\(^2\) and log transformed.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>( C_{\text{max}}\text{(before)}: C_{\text{max}}\text{(after)}^a )</th>
<th>( t_{\text{max}}\text{(before)}: t_{\text{max}}\text{(after)}^b )</th>
<th>( \text{AUC}<em>{0-\infty}\text{(before)}: \text{AUC}</em>{0-\infty}\text{(after)}^c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capcitabine</td>
<td>2.47 (1.61-3.78) 0.50 (0.020) 1.51 (1.28-1.79)</td>
<td>1.81 (1.34-2.43) 0.32 (0.004) 1.26 (1.02-1.54)</td>
<td>1.53 (1.05-2.22) 0.50 (0.012) 1.15 (0.99-1.33)</td>
</tr>
<tr>
<td>5'-DFCR</td>
<td>1.58 (1.06-2.37) 0.25 (0.002) 1.13 (0.93-1.36)</td>
<td>1.26 (1.02-1.57) 0.67 (0.016) 1.07 (0.86-1.33)</td>
<td>1.11 (1.01-1.22) 0.67 (0.020) 1.05 (0.84-1.15)</td>
</tr>
<tr>
<td>5-FU</td>
<td>1.26 (1.02-1.57) 0.67 (0.016) 1.07 (0.86-1.33)</td>
<td>1.11 (1.01-1.22) 0.67 (0.020) 1.05 (0.84-1.15)</td>
<td></td>
</tr>
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</table>

\( ^a \) Ninety % confidence interval given in parentheses.
\( ^b \) Median of the ratios; \( \rho \) (Wilcoxon test) given in parentheses.
\( ^c \) Primary pharmacokinetic parameter as defined in “Materials and Methods.”

The results on concentration-effect relationships that would allow us to predict the clinical consequences of taking the drug before food intake, it is recommended to continue to take capcitabine after food (within 30 min after food intake), because all clinical studies conducted thus far followed this recommendation.

The findings of this study are the opposite to what was expected based on in vitro experiments that showed that capcitabine is unstable at low pH (19% degradation in 30 min at pH 1.2). In fasted conditions, the gastric pH is low (median, 1.8; 50th, 2.9; 75th, 3.2). Because capcitabine is unstable at low pH, it is recommended to continue to take capcitabine after food (within 30 min after food intake), because all clinical studies conducted thus far followed this recommendation.

Conclusion. Fasted conditions increase both the rate and extent of capcitabine absorption. The food effect on pharmacokinetics is less and less pronounced as one examines the metabolites in their order of formation (5'-DFCR \( \rightarrow \) 5'-DFUR \( \rightarrow \) 5-FU \( \rightarrow \) FULH \( \rightarrow \) FBAL). Food has a minor effect on \( \text{AUC}_{0-\infty} \) of the three main metabolites in plasma (5'-DFUR, 5-FU, and FBAL). Detailed information on the relationship between concentration and safety/efficacy is necessary to evaluate the clinical significance of these pharmacokinetic findings. At present, it is recommended that capcitabine is administered within 30 min after food intake because this was the procedure used in the clinical trials.

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