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Influence of the antacid Maalox on the pharmacokinetics of capecitabine in cancer patients

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Abstract *Purpose*: In the present study the possible influence of the antacid Maalox on the pharmacokinetics of capecitabine (Xeloda) and its metabolites was investigated in cancer patients. *Methods*: A total of 12 patients with solid, predominantly metastatic tumors of various origin received a single oral dose of 1250 mg/m^2 of capecitabine (treatment A), a single oral dose of 1250 mg/m^2 of capecitabine followed immediately by 20 ml of Maalox (treatment B), and a single oral dose of 1250 mg/m^2 of capecitabine followed 2 h later by 20 ml of Maalox (treatment C) in an open, randomized, three-way cross over fashion. Serial blood and urine samples were collected for up to 24 h after each administration. Unchanged capecitabine and its metabolites were analyzed in plasma using liquid chromatography/mass spectrometry and in urine using nuclear magnetic resonance spectroscopy. *Results*: Administration of Maalox either concomitantly with capecitabine or delayed by 2 h did not influence the time to peak plasma concentrations (C_{max}) or the elimination half-lives of capecitabine and its metabolites. Unexpectedly, moderate increases in the C_{max} and $AUC_{0-\infty}$ values obtained for capecitabine and 5′-deoxy-5-fluorocytidine were observed when Maalox was given together with capecitabine. However, these increases, which ranged between 10% and 31%, were not statistically significant ($P > 0.05$) and are not of clinical significance. There was no indication of consistent changes in the plasma concentrations of the other metabolites 5′-deoxy-5′-fluorouridine (5′-DFUR), 5-fluorouracil, and α-fluoro-β-alanine. The C_{max} and $AUC_{0-\infty}$ values recorded for these three metabolites increased and decreased in a stochastic manner. The magnitude of these changes was low (<13%) and not statistically significant. The primary statistical analysis of the $AUC_{0-\infty}$ obtained for 5′-DFUR provided a P value of 0.4524 and clearly indicated no significant difference between the treatments. The addition of Maalox had no influence on the overall urinary recovery or the proportion of the dose recovered as capecitabine or its metabolites from urine. *Conclusion*: At the dose used in this study, the effect of concomitantly delivered Maalox on the extent and rate of gastrointestinal absorption of capecitabine is not clinically significant. Therefore, there is no need to adjust the dose or timing of capecitabine administration in patients treated with Maalox.

Key words Capecitabine · Pharmacokinetic interaction · Maalox · 5-Fluorouracil

Abbreviations *5′-DFCR* 5′-Deoxy-5-fluorocytidine · *5′-DFUR* 5′-Deoxy-5-fluorouridine · *5-FU* 5-Fluorouracil · FUH_2 Dihydro-5-fluorouracil · *FBAL* α-Fluoro-β-alanine · *FUPA* 5-Fluoro-ureido-propionic acid · *p-FPA* *p*-Fluoro-D-phenylalanine · *LC/MS-MS* Liquid chromatography/mass spectrometry · *NMRS* Nuclear magnetic

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resonance spectroscopy ·
HPLC High-performance liquid chromatography ·
CV Coefficient of variation ·
RSD Relative standard deviation · *DEV* Deviation ·
QC Quality control · *NCIC* National Cancer Institute of Canada · *CTC* Common toxicity criteria

Introduction

The novel fluoropyrimidine carbamate capecitabine (Xeloda) is an orally available precursor of 5′-deoxy-5-fluorouridine (5′-DFUR) that offers the opportunity for oral home-based patient administration of an antineoplastic drug. The activity of capecitabine in common solid tumors such as colorectal and breast cancer has been demonstrated with a favorable safety profile [1, 2]. In humans, capecitabine is rapidly and extensively absorbed with low interpatient variability following oral administration. It is first extensively metabolized in the liver to 5′-DFCR by hepatic carboxylesterase. This metabolite is then converted to 5′-DFUR by cytidine deaminase, located in high concentrations in many human tumor tissues as well as in healthy liver tissue. Subsequent catalytic activation of 5′-DFUR to the cytotoxic agent 5-FU occurs selectively at the tumor site by the tumor-associated angiogenic factor thymidine phosphorylase [3]. In a pharmacokinetic study in colorectal cancer patients requiring tumor resection, concentrations of 5-FU were 3.2 times higher in primary colorectal tumor tissue as compared with adjacent healthy tissue and 14 times higher than those achieved in plasma [4]. Capecitabine and its intermediates themselves are not cytotoxic but become effective only after conversion to 5-FU in human cancer cells. As described previously in the literature, 5-FU is further catabolized to FUH_2, FUPA, and FBAL [5].

Most of the antacids on the market, such as Maalox, contain magnesium hydroxide and aluminum hydroxide as active ingredients. Concomitant administration of these antacids with other drugs can result in a drastic reduction in the gastrointestinal absorption of the latter. For example, coadministration of antacids has reduced the bioavailability of certain fluorinated quinolones and tetracyclines by more than 90% [6–8]. Formation of stable chelates, adsorption to the aluminum/magnesium hydroxide gel, and/or the increase in gastric pH caused by the antacids are the reasons for the observed reduction in drug absorption. In vitro experiments have shown that Maalox or aluminum hydroxide considerably decreases the dissolution and delays the disintegration of capecitabine tablets (Odaki et al., unpublished data on file at F. Hoffmann-La Roche). As antacids are a frequent comedication in the capecitabine target-patient population, it was mandatory that the effect of magnesium/aluminum hydroxide on the pharmacokinetics of capecitabine and its metabolites be investigated.

Patients and methods

Patients

A total of 13 patients with histologically or cytologically confirmed solid tumors were enrolled in this study. One patient withdrew before the third treatment for personal reasons. These patients had not received cytotoxic chemotherapy or radiation therapy within 4 weeks of the start of the study. They were hospitalized for 24 h on the days of drug administration and sample collection at three different centers: Aberdeen Royal Infirmary in Aberdeen, United Kingdom; Western General Hospital NHS Trust in Edinburgh, United Kingdom; and Roche Clinical Pharmacology Unit in Strasbourg, France. Seven women and five men were evaluable for pharmacokinetics. The patients were aged 35–74 years (mean 55.7 years) and weighed 50–98 kg (mean 71 kg), their body surface area was 1.60–2.16 m^2 (mean 1.78 m^2), and their Karnofsky performance status ranged between 70% and 100% (median 80%). At baseline the following tumors were diagnosed: metastatic colon cancer ($n = 8$), nonmetastatic colon cancer, metastatic gastric cancer, nonmetastatic pancreatic cancer, and metastatic cancer of unknown origin ($n = 1$ each).

Clinical procedure

This was a single-dose, open-label, three-way crossover, randomized trial performed in three centers. The study was conducted in full agreement with the EC guidelines for good clinical practice and according to the revised Declaration of Helsinki. Informed consent was obtained from all subjects prior to the start of the study and the protocol was approved by the local ethical review boards. Screening at study start included physical examination, medical history, vital signs, ECG, laboratory safety tests (hematology, serum biochemistry, urinalysis), and evaluation of the Karnofsky performance status. During treatment, vital signs, laboratory parameters, and adverse events were assessed. All patients had to meet carefully selected inclusion/exclusion criteria taking into account the stage of the disease, current medical status, and life expectancy.

Patients were randomly assigned to the treatment sequences consisting of a combination of treatments A, B, and C. At 30 min after a standard meal the patients received 1250 mg/m^2 of capecitabine given as a single oral dose (treatment A), a single oral dose of 1250 mg/m^2 of capecitabine followed immediately by 20 ml of Maalox suspension (treatment B), and a single oral dose of 1250 mg/m^2 of capecitabine followed 2 h later by 20 ml of Maalox suspension (treatment C). The effect of Maalox was investigated after postprandial administration of capecitabine according to the recommendation of the manufacturer [9]. The washout period between the three administrations was 6–8 days. Capecitabine was given in the form of film-coated 150- and 500-mg tablets. Maalox was given as an oral suspension containing 39 mg magnesium hydroxide plus 44 mg aluminum hydroxide per milliliter. Correct intake of the drug was supervised by the responsible medical staff.

Blood samples (5 ml) for pharmacokinetic evaluation were collected in Vacutainers containing ethylenediaminetetraacetic acid (EDTA) as a anticoagulant at the following time points: predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 h following capecitabine administration. Blood samples were centrifuged and the supernatant plasma was removed and stored in plastic tubes at −20 °C until analysis. Urine samples for determination of capecitabine and its metabolites were collected prior to drug administration and at intervals of 0–12 and 12–24 h after each administration.

Analytical assay

Plasma samples, calibration standard samples, and quality-control (QC) samples were analyzed for capecitabine and its metabolites (5′-DFCR, 5′-DFUR and 5-FU) using high-performance liquid chromatography (HPLC) with turbo-ion-spray/tandem mass

spectrometry (LC/MS-MS) [9]. Samples containing FBAL were analyzed using HPLC with ion-spray/tandem mass spectrometry (LC/MS-MS). A 0.5-ml aliquot of the plasma sample was mixed with 50 µl of internal standard solution to yield final concentrations of 1–10 µg/ml. [^{13}C, $^{15}N_2$]-capecitabine, [^{13}C, $^{15}N_2$]-5′-DFCR, and [$^{15}N_2$]-5′-DFUR were used as the internal standards for capecitabine, 5′-DFCR, and 5′-DFUR, respectively. [$^{15}N_2$]-5-FU was used as the internal standard for 5-FU, and β-alanyl-alanine was used as the internal standard for FBAL. Samples were deproteinized by the addition of 1 ml CH_3CN and centrifuged. Subsequently the supernatant was mixed with 100 µl of 65 m*M* acetic acid, dried under nitrogen, and reconstituted with 100 µl of 0.65 m*M* acetic acid. The solution was applied to an Isolute C_{18} extraction cartridge column conditioned with 1 ml MeOH and then 3 ml of water. The sample was eluted with 1 ml of 2 m*M* ammonium acetate (fraction A, for determination of 5-FU and FBAL) followed by 0.75 m*M* MeOH (fraction B, for determination of capecitabine, 5′-DFCR, and 5′-DFUR), and both fractions were then dried. The residue of fraction A was dissolved in 100 µl water and an aliquot of 20 µl was injected into the chromatography system for analysis of 5-FU. The residue of fraction B was redissolved in 10 m*M* ammonium acetate.

After filtration of the solution a 25-µl aliquot was injected for simultaneous analysis of capecitabine, 5′-DFCR, and 5′-DFUR. Capecitabine, 5′-DFCR, and 5′-DFUR were chromatographed using a 2.1 × 150-mm Supelcosil ABZ + C_{18} column and a gradient mobile phase containing 10 m*M* ammonium formate: acetonitrile. 5-FU was chromatographed using a 2.0 × 150-mm YMC J′Sphere M80 C_{18} column and a mobile phase containing 10:90 methanol: 5 m*M* ammonium formate. FBAL (eluted in fraction A) was derivatized using 2-methoxy-2,4-diphenyl-3(2H)-furanone and was chromatographed using a 4.6 × 150-mm YMC J′Sphere M80 C_{18} column and a mobile phase containing 60:40 methanol: 5 m*M* ammonium formate. β-Alanyl-alanine was used as the internal standard for FBAL. Flow rates were 0.8–1.0 ml/min.

The plasma calibration concentration range was 0.01–5.00 µg/ml for capecitabine and 5′-DFCR, 0.05–25.0 µg/ml for 5′-DFUR, 0.002–1.00 µg/ml for 5-FU, and 0.020–10.0 µg/ml for FBAL. The overall between-day variabilities (%RSD) of the QC samples were < 4% for capecitabine, < 5% for 5′-DFCR and 5′-DFUR, < 8% for 5-FU, and < 15% for FBAL. The QC deviations from nominal concentrations (%DEV) were within 2% for capecitabine, within 1% for 5′-DFCR, within 11% for 5′-DFUR, within 9% for 5-FU, and within 8% for FBAL. The overall between-day variabilities of the calibration standards were < 4% for capecitabine, < 3% for 5′-DFCR, < 5% for 5′-DFUR, < 7% for 5-FU, and < 8% for FBAL. The calibration standard deviations from nominal concentrations were within 3% for capecitabine and for 5′-DFCR, within 11% for 5′-DFUR, within 3% for 5-FU, and within 8% for FBAL. The lower limit of quantification for capecitabine, 5′-DFCR, and 5′-DFUR was 0.05 µg/ml using 0.5 ml of human plasma. For 5-FU and FBAL the lower limit of quantification was 0.003 and 0.02 µg/ml, respectively.

Urine samples (5-ml aliquots) were concentrated by centrifuging evaporation at 40 °C to < 0.5 ml. Next, 0.5 ml of internal standard solution was added to the concentrated sample (1 µmol p-FPA/sample). The sample was made up to 1 ml with water and then sonicated and, subsequently, the pH was adjusted to 6–7 using formic acid. Following centrifugation at 1500 *g* for 10 min, 0.6 ml of supernatant was transferred to an NMR sample tube for analysis. [^{19}F]-NMR spectra were recorded at 399.65 MHz and run without proton decoupling. The peak positions were referenced to an external standard, trifluoroacetic acid. The instrumental settings were established as follows: probe temperature, RT; pulse width, 5.5 µs (40 °C); recycling time, 5 s; number of scans, 5000 or 2500; computer resolution, 5 Hz/point; line broadening caused by exponential multiplication, 5 Hz. The typical shifts for p-FPA, capecitabine, 5′-DFCR, 5′-DFUR, 5-FU, FUH_2, FUPA, and FBAL were −40.5, −86.2, −89.8, −90.5, −94.6, −123.5, −110.5, and −111.6 ppm, respectively.

The interassay precision determined from QA samples (%CV) was 4.91% for capecitabine, 5.84% for 5′-DFUR, 5.99% for 5-FU, and 6.21% for FBAL. The lower limit of quantification for capecitabine, 5′-DFCR, 5′-DFUR, 5-FU, FUH_2, and FBAL was 0.02 µmol/ml using 5 ml urine. Under the same conditions the lower limit of quantification for FUPA was 0.05 µmol/ml.

Pharmacokinetic evaluation

Estimation of the pharmacokinetic parameters of capecitabine and its metabolites (5′-DFCR, 5′-DFUR, 5-FU, and FBAL) was performed from the concentration-time data using non-compartmental methods [10]. The following parameters were estimated: the maximal plasma concentration (C_{max}) and the time of its occurrence (t_{max}) were determined from the observed highest concentration and its time of occurrence, respectively. The apparent elimination half-life ($t_{1/2}$) 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. The area under the plasma concentration-time curve extrapolated from time 0 to infinity ($AUC_{0-\infty}$) was estimated from the sum of AUC_{0-t} and $C_{t\ last}$/k. AUC_{0-t} is the area under the curve from time 0 to the last sampling time (t_{last}) at which the concentration could be measured ($C_{t\ last}$). AUC_{0-t} was estimated using the linear trapezoidal rule. From the urine concentrations of capecitabine, 5′-DFCR, 5′-DFUR, 5-FU, FUH_2, FUPA, and FBAL, the percentage of each dose recovered in urine was estimated.

Statistical analysis

Descriptive statistics were used to summarize the pharmacokinetic parameters. Geometric mean values and geometric CVs are reported for C_{max} and $AUC_{0-\infty}$; arithmetic mean values and CVs, for $t_{1/2}$; and median, minimal, and maximal values, for t_{max}. With regard to comparative statistics, the primary parameter for the assessment of the interaction with Maalox was the $AUC_{0-\infty}$ recorded for the analyte 5′-DFUR. A three-way analysis of variance (ANOVA) with the factors subject, period, and treatment was performed on the log-transformed variables (PROC GLM, SAS 6.12). The ratios of the effects of treatments B and C to treatment A for the original variables were estimated. The 95% confidence limits were calculated by exponentiation of the corresponding results of the ANOVA, and this statistical parameter was used to judge the clinical relevance of the interaction. Other pharmacokinetic parameters were regarded as secondary. The analysis was repeated for the log-transformed C_{max} noted for 5′-DFUR and, in additional analyses, for the log-transformed AUC and C_{max} recorded for capecitabine, 5-FU, 5′-DFCR, and FBAL. These results were interpreted in an exploratory sense only. All comparisons were made at the significance level $\alpha = 0.05$.

Results

Pharmacokinetics

The pharmacokinetic plasma profiles (arithmetic mean concentration values versus time) obtained after the administration of 1250 mg/m^2 of capecitabine alone and together with Maalox are shown for capecitabine and the primary metabolite 5′-DFUR in Figs. 1 and 2, respectively. Concomitant administration of Maalox resulted in a moderate increase or decrease in the mean plasma concentrations (as reflected by the C_{max} and AUC values) and in a slight reduction in the t_{max} values recorded for these two compounds. Similar findings were obtained for 5′-DFCR, 5-FU, and FBAL (mean profiles not shown).

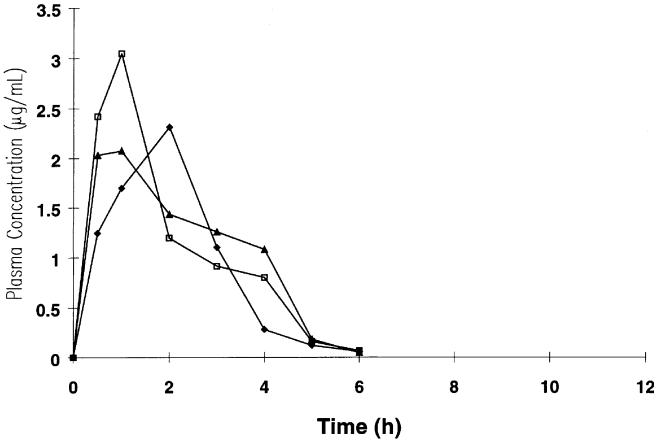

Fig. 1 Plasma concentrations of capecitabine determined following a single oral dose of 1250 mg/m^2 given alone (treatment A, -◆-) or immediately followed by 20 ml of Maalox (treatment B, -□-) and 20 ml of Maalox given 2 h after capecitabine (treatment C, -▲-). Concentrations are presented as arithmetic mean values recorded for 12 subjects

Descriptive statistics on the pharmacokinetic parameters (including urinary recovery) of capecitabine and its metabolites 5′-DFCR, 5′-DFUR, 5-FU, and FBAL as estimated after the administration of 1250 mg/m^2 of capecitabine alone, after the administration of 1250 mg/m^2 of capecitabine followed immediately by Maalox, and after the administration of 1250 mg/m^2 of capecitabine followed 2 h later by Maalox are presented in Table 1. Comparative statistics on the log-transformed parameters C_{max} and $AUC_{0-\infty}$ as recorded for capecitabine and its metabolites are shown in Table 2.

Following oral administration, peak concentrations of capecitabine were achieved rapidly. There was a trend toward a more rapid absorption following treatment B and toward a slower absorption following treatment C, but the ranges of t_{max} were similar following all three treatments. The elimination half-life of capecitabine was almost identical following all three treatments. AUC and C_{max} values noted for capecitabine were increased by the addition of Maalox. Relative to treatment A, C_{max} and $AUC_{0-\infty}$ values increased by 18% and 10% following treatment B and by 17% and 7% following treatment C, respectively. The interpatient variability of capecitabine concentrations also increased with the addition of Maalox (Table 1).

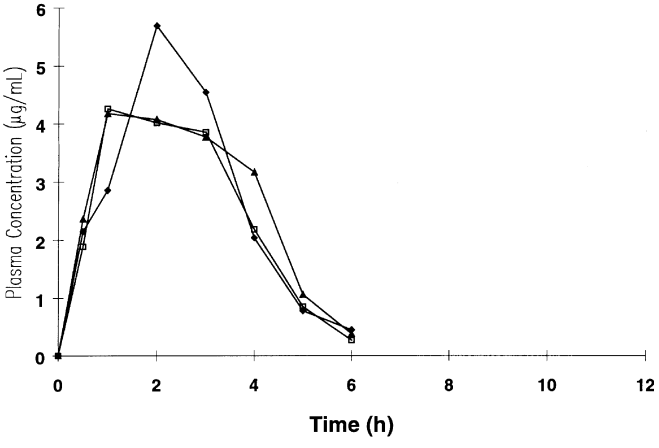

Fig. 2 Plasma concentrations of 5′-DFUR determined following a single oral dose of 1250 mg/m^2 of capecitabine given alone (treatment A, -◆-) or immediately followed by 20 ml of Maalox (treatment B, -□-) and 20 ml of Maalox given 2 h after capecitabine (treatment C, -▲-). Concentrations are presented as arithmetic mean values recorded for 12 subjects

Similar increases in plasma concentrations were observed for 5′-DFCR following treatments B and C. Relative to treatments A, C_{max} and $AUC_{0-\infty}$ values increased by 25% and 23% following treatments B and by 31% and 21% following treatment C, respectively. No change was observed for t_{max} or for the elimination half-life (Table 1). No major change was detected in the C_{max}, $AUC_{0-\infty}$, t_{max}, or $t_{1/2}$ values recorded for 5′-DFUR following treatments B and C (Table 1).

Following oral administration of capecitabine, peak concentrations of 5-FU were achieved rapidly and there was no difference in the t_{max} values noted following the three treatments. The half-life of 5-FU appeared to be lower following the addition of Maalox. However, the higher mean value and the increase in variability observed following treatment A were due to a single high value of 5.3 h obtained in one patient. Following treatments B and C the same subject had an estimated half-life of 0.57 and 0.61 h, respectively. The concentrations of 5-FU were similar following the three treatments. Only a small decrease of 9% in C_{max} and of 13% in AUC was seen following treatment B, and a small increase of 10% in C_{max} with no change in AUC was noted following treatment C (Table 1). No major change in the pharmacokinetic parameters of FBAL occurred on coadministration of Maalox, except for an increase in C_{max} of only 7% following treatment C (Table 1).

A summary of the urinary excretion (percentage of the capecitabine dose recovered) following the three treatments is shown in Table 1. Overall, 73%, 81%, and 73% of the dose was recovered following treatments A, B, and C, respectively (including recovery of metabolites FUH_2 and FUPA). As shown in Table 1, the majority of the dose was recovered as FBAL (51%, 56%, and 51%, respectively), with all other compounds making a minor contribution.

Statistical results

For the primary parameter $AUC_{0-\infty}$ of 5′-DFUR the estimates from the ANOVA of the effect of Maalox are presented in Table 2. For 5′-DFUR the estimated $AUC_{0-\infty}$ was 5% lower and 2% higher when Maalox was given immediately after capecitabine or 2 h later, respectively, as compared with administration of capecitabine alone.

The 95% confidence intervals recorded for the relative effect of Maalox are presented in Table 2. They are quite narrow and even fall within the usual

Table 1 Descriptive statistics of the pharmacokinetic parameters of capecitabine and its metabolites in 12 patients after oral administration of 1250 mg/m^2 of capecitabine alone (treatment A) or immediately followed by 20 ml of Maalox (treatment B) and 20 ml of Maalox given 2 h after capecitabine (treatment C). Geometric mean values (CV%) are reported for C_{max} and $AUC_{0-\infty}$. Median values (min-max) are reported for t_{max}. Arithmetic mean values (CV%) are reported for $t_{1/2}$ and urinary recovery (given as % of capecitabine dose). Total urinary recovery includes the analysis of two additional capecitabine metabolites, FUH_2 and FUPA

	Treatment A	Treatment B	Treatment C
Capecitabine:			
C_{max} (μg/ml)	3.49 (52%)	4.13 (80%)	4.07 (66%)
$AUC_{0-\infty}$ (μg ml^{-1} · h)	5.48 (37%)	6.03 (52%)	5.84 (51%)
t_{max} (h)	2.0 (0.5–3.0)	1.0 (0.5–4.0)	2.5 (0.5–4.0)
$t_{1/2}$ (h)	0.55 (45%)	0.51 (31%)	0.47 (37%)
Urinary recovery (%)	2.57 (43%)	2.80 (38%)	2.57 (35%)
5′-DFCR:			
C_{max} (μg/ml)	2.81 (82%)	3.52 (73%)	3.69 (44%)
$AUC_{0-\infty}$ (μg ml^{-1} · h)	6.51 (77%)	7.98 (67%)	7.89 (40%)
t_{max} (h)	2.0 (0.5–4.0)	1.5 (0.5–5.0)	2.0 (0.5–4.0)
$t_{1/2}$ (h)	0.77 (23%)	0.76 (20%)	0.78 (19%)
Urinary recovery (%)	7.45 (64%)	7.24 (30%)	6.45 (29%)
5′-DFUR:			
C_{max} (μg/ml)	7.35 (45%)	7.21 (45%)	8.01 (45%)
$AUC_{0-\infty}$ (μg ml^{-1} · h)	16.0 (38%)	15.3 (23%)	16.2 (28%)
t_{max} (h)	2.0 (0.5–4.0)	2.0 (0.5–4.0)	2.5 (1.0–4.0)
$t_{1/2}$ (h)	0.67 (24%)	0.66 (19%)	0.71 (49%)
Urinary recovery (%)	7.32 (51%)	9.54 (30%)	8.36 (31%)
5-FU:			
C_{max} (μg/ml)	0.289 (89%)	0.263 (84%)	0.319 (89%)
$AUC_{0-\infty}$ (μg ml^{-1} · h)	0.620 (73%)	0.540 (60%)	0.614 (79%)
t_{max} (h)	2.0 (0.5–4.0)	2.0 (0.5–4.0)	2.5 (0.5–4.0)
$t_{1/2}$ (h)	1.15 (124%)	0.64 (23%)	0.63 (23%)
Urinary recovery (%)	0.671 (59%)	0.666 (46%)	0.639 (41%)
FBAL:			
C_{max} (μg/ml)	6.68 (22%)	6.93 (16%)	7.15 (20%)
$AUC_{0-\infty}$(μg ml^{-1} · h)	38.8 (31%)	37.7 (28%)	38.4 (29%)
t_{max} (h)	3.5 (2.0–5.1)	3.0 (2.0–5.0)	3.5 (2.0–5.0)
$t_{1/2}$ (h)	4.19 (11%)	4.21 (12%)	4.22 (11%)
Urinary recovery (%)	51.3 (29%)	56.1 (18%)	51.0 (23%)
Total urinary recovery (% of dose)	73.2 (28%)	80.5 (15%)	72.8 (21%)

bioequivalence region of 80–125%. The period effect (*P* value 0.0185) was significant at the significance level of 0.05. As compared with period 1, the $AUC_{0-\infty}$ of 5′-DFUR was 20% and 12% higher in periods 2 and 3, respectively. No interaction between treatment and period was found (*P* value 0.774). No reason for the period effect could be found. Since each treatment was given nearly equally often in each period, possible period effects should only slightly affect the estimation of the treatment effects. Similar results were obtained when the same analysis was repeated for the untransformed primary parameter $AUC_{0-\infty}$ of 5′-DFUR.

Table 2 Estimates of the effect of Maalox on the $AUC_{0-\infty}$ and C_{max} values recorded for capecitabine and its metabolites as determined by ANOVA. The 5′-DFUR $AUC_{0-\infty}$ is the primary parameter for the interaction assessment

Analyte	Treatment	$AUC_{0-\infty}$			C_{max}		
		Estimate[a]	95% Confidence interval		Estimate[a]	95% Confidence interval	
Capecitabine	A	100	–	–	100	–	–
	B	108	83	139	114	76	169
	C	109	84	140	121	81	180
5′-DFCR	A	100	–	–	100	–	–
	B	120	94	153	121	89	165
	C	124	97	158	136	100	185
5′-DFUR	A	100	–	–	100	–	–
	B	95	84	107	97	77	121
	C	102	90	115	110	88	138
5-FU	A	100	–	–	100	–	–
	B	89	72	111	89	63	125
	C	101	81	125	112	80	158
FBAL	A	100	–	–	100	–	–
	B	98	92	106	103	95	112
	C	100	93	107	107	99	116

[a] Expressed in % relative to the reference treatment (treatment A)

The results recorded for the $AUC_{0-\infty}$ of capecitabine and the other metabolites and for the secondary variable C_{max} are also shown in Table 2. The differences between treatments were not statistically significant. For 5′-DFCR the estimated C_{max} was 21% and 36% higher when Maalox was given immediately after capecitabine or 2 h later as compared with administration of capecitabine alone. For the $AUC_{0-\infty}$ of 5′-DFCR these estimates were 20% and 24%, respectively.

Discussion

The primary objective of this study was to investigate the possible influence of Maalox on the pharmacokinetics of capecitabine and its metabolites in cancer patients. Maalox is a liquid antacid and, like most antacids on the market, contains aluminum hydroxide and magnesium hydroxide as active ingredients. Concomitant administration of these antacids can result in a clinically significant reduction or delay in the gastrointestinal absorption of certain antibiotics, ferrous salts, sodium fluoride, and theophylline, among other substances [6–8, 11]. For example, coadministration of Maalox has reduced the bioavailability of tetracyclines and of fluorinated quinolones such as norfloxacin and ciprofloxacin by more than 90% [6–8]. The formation of stable chelates between the coadministered drugs and the magnesium/aluminum ions of the antacid, which are much more slowly absorbed, if at all, is the primary reason for this effect. In addition, adsorption to the aluminum/magnesium hydroxide gel formed in the stomach and the increase in gastric pH caused by the antacid may be responsible for the observed reduction in drug absorption. For the circumvention of a decrease in bioavailability and, hence, in clinical efficacy, it is generally recommended that antacids be given at least 2 h before or after drug intake or that the antacids be replaced by H_2-receptor antagonists such as cimetidine or ranitidine. In vitro experiments have shown that Maalox or aluminum hydroxide causes a prolongation of the complete dissolution of capecitabine tablets in artificial gastric juice from 50 min to >100 min and a delay in the disintegration time from approximately 20 to 40 min [9]. As antacids are a frequent comedication in the capecitabine target-patient population, it was mandatory that the effect of magnesium/aluminum hydroxide on the gastrointestinal absorption of capecitabine be investigated.

The results of this study indicated that coadministration of the recommended standard dose of 20 ml of Maalox either immediately or delayed by 2 h did not influence the time to peak plasma concentrations or the elimination half-lives of capecitabine and its metabolites. Unexpectedly, both the C_{max} and $AUC_{0-\infty}$ values recorded for capecitabine and 5′-DFCR were moderately increased when Maalox was combined with capecitabine (treatments B and C). However, these increases were not statistically significant ($P > 0.05$) and are not of clinical significance. For the C_{max} and $AUC_{0-\infty}$ values noted for 5′-DFUR, 5-FU, and FBAL, there was no indication of consistent changes in the plasma concentrations. Both increases and decreases in C_{max} and $AUC_{0-\infty}$ were recorded in a stochastic manner. The magnitude of these changes was small (< 13%) and not statistically significant ($P > 0.05$). In the primary statistical analysis of the $AUC_{0-\infty}$ of 5′-DFUR the relative changes from treatment A were estimated as 95% (95% CI 85–107%) for treatment B and as 102% (95%CI 90–115%) for treatment C. Both estimates and the narrow confidence intervals indicated no clinically relevant difference between the treatments. Because a nearly balanced crossover design was used, the significant period effect ($P = 0.0185$) did not influence this result. The kinetic results obtained from the plasma concentration are further supported by the urinary excretion of capecitabine and its metabolites following the three treatments. Concomitant or delayed addition of 20 ml Maalox had no influence on the total urinary recovery or the proportion of the dose recovered as each analyte.

This study used the recommended dose of Maalox and showed no significant effect on the absorption of capecitabine. In contrast, the in vitro experiments suggested a possible effect on the absorption of capecitabine (Odaki et al., unpublished data on file at F. Hoffmann-La Roche). The effect of Maalox on the dissolution and disintegration of capecitabine tablets in vitro was observed at magnesium and aluminum hydroxide concentrations that would not be reached in the gastrointestinal tract of patients receiving the recommended dose regimen of Maalox. The conclusions of this study are valid at the recommended dose of Maalox, and it is important that we emphasize the correct dosing of Maalox to patients on its combination with capecitabine.

In conclusion, concomitant administration of the recommended standard dose of Maalox did not decrease the absorption of capecitabine from the gastrointestinal tract. The rate of absorption of capecitabine was not affected as judged by the t_{max} values, and the apparent minor increase in the extent of absorption as judged by the AUC values was not of clinical significance. The effect of Maalox on the pharmacokinetics of capecitabine is not clinically significant, and there is therefore no need to adjust the dose and timing of capecitabine administration in patients treated with Maalox.

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