The Effect of Food on the Pharmacokinetics of S-1 after Single Oral Administration to Patients with Solid Tumors


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ABSTRACT

Purpose: The purpose is to determine the effect of food on the bioavailability of S-1, an oral formulation of the 5-fluorouracil (5FU) prodrug Flora�ar (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), a dihydropyrimidine dehydrogenase inhibitor, and oxonic acid (an inhibitor of 5FU phosphorylation in normal gut mucosa) in a molar ratio of 1:0.4:1.

EXPERIMENTAL DESIGN: Eighteen patients received a single dose of S-1 of 35 mg/m² with (535–885 kcal) or without food in a crossover study design: in arm A without breakfast on day 7 and with breakfast on day 0 and in arm B the reversed sequence. Blood samples were taken before and after S-1 administration. This food effect was evaluated according to the Food and Drug Administration guidelines using log-transformed data.

RESULTS: Pharmacokinetic parameters for 5FU without breakfast were as follows: Tmax, 107 min; Cmax, 1.60 µM; area under the plasma concentration-time curve (AUC) 441 µM × min; and T1/2, 104 min. Fasting decreased Tmax of FT, 5FU, CDHP, and oxonic acid significantly (P < 0.006) and increased the Cmax (P < 0.013). The food/fast ratio for the AUC of FT was not different, which for 5FU was 0.84 (P = 0.041), for CDHP was 0.89 (P = 0.191), for oxonic acid was 0.48 (P < 0.0005), and for cyanuric acid, the breakdown product of oxonic acid, was 5.1 (P = 0.019). Accumulation of uracil, indicative for dihydropyrimidine dehydrogenase inhibition, was not affected, as well as the T1/2 of FT, 5FU, CDHP, and oxonic acid. Evaluation of the log-transformed data demonstrated that the 90% confidence interval for the food/fast ratio for the Cmax and AUC of FT, 5FU, CDHP, and uracil were within 70–143% and 80–125%, respectively, indicating no food effect. Only for oxonic acid and cyanuric acid were these values outside this interval.

CONCLUSIONS: Food intake affected only the pharmacokinetics of the S-1 constituent oxonic acid but not of FT, CDHP, and 5FU. Because oxonic acid is included to protect against gastrointestinal toxicity, this observation might affect the gastrointestinal toxicity and thus the efficacy of S-1.

INTRODUCTION

The use of oral administration of anticancer agents is increasing. When the efficacy of classical venous administration and oral administration was similar, patients prefer the oral formulation (1). Several novel oral formulations of fluoropyrimidines (2) do not have the disadvantages of earlier oral administrations of 5-fluorouracil (5FU) such as a low and unpredictable bioavailability caused by a variable stability of the drug in the gastrointestinal tract, an incomplete and variable resorption from the intestine, and an extensive breakdown of 5FU by both gastrointestinal microflora and by human enzymes (3). This is enabled by the use of stable prodrugs of 5FU and inhibitors of dihydropyrimidine dehydrogenase (DPD), the first enzyme responsible for 5FU degradation (2). These prodrugs also enable a potential tissue and tumor-selective activation such as with capcitabine, which requires a multistep activation, catalyzed by esterases, cytidine deaminase, and at last by thymidine phosphorylase (4). This last enzyme has a high expression in tumors (5). Another group of drugs combines 5FU (or a 5FU prodrug) with an inhibitor of DPD. Eniluracil (EU), a suicide inhibitor of DPD, is combined with 5FU itself (2, 6). In the formulations uracil-tegafur and S-1, a 5FU prodrug, Flora�ar (FT), is combined with a reversible inhibitor of DPD, either uracil in the formulation uracil-tegafur and S-1, a 5FU prodrug, Flora�ar (FT), is combined with a reversible inhibitor of DPD, either uracil in the formulation uracil-tegafur (in a molar ratio of 1:4; Ref. 7) or 5-chloro-2,4-dihydroxypyridine (CDHP) in the formulation S-1 (8). The latter formulation also contains oxonic acid, which specifically accumulates in the gut inhibiting phosphorylation to the active metabolite fluorouridine monophosphate (9). All formulations have shown a comparable antitumor effect compared with i.v. formulations, although disease-specific differences exist.

The pharmacokinetics of oral 5FU formulations have been described extensively (10–17). For the three formulations with a DPD inhibitor, the highest 5FU concentrations were found after 5FU-EU (13). Food may interfere with absorption significantly. Administration of food with oral 5FU-EU slowed the absorption of 5FU and decreased the Cmax but did not affect the AUC (15). For capcitabine, the effect of food varied for the various metabolites. It was most pronounced for the parent compound capcitabine but moderate for 5’-deoxy-5-fluorocytidine, the first metabolite. However, only a minor effect was
were as follows: time point of maximum observed concentration in plasma (Tmax); concentration in plasma corresponding to Tmax (Cmax); terminal half-life (T1/2); area under the plasma concentration versus time (C-t) curve extrapolated to infinity (AUCINF); and the mean residence time extrapolated to infinity (MRTINF). The terminal half-life was calculated from the terminal elimination rate constant: y. This rate constant was calculated by means of linear regression of the final part of the ln C-t curve. The final half-life could be calculated by \( T_{1/2} = -\ln (2)/y = -0.693/y \).

For the calculation of the elimination rate constant, we used the three final concentrations of the C-t curve (4, 8, and 24 h). The AUCINF was calculated by the logarithmic trapezoidal rule from the start to infinity. Extrapolation from the predicted last plasma concentration was carried out using the following equation:

\[
AUC_{INF} = AUMC_{INF}/AUC_{INF}. 
\]

The mean residence time extrapolated to infinity (MRTINF) was calculated by MRTINF = AUMCINF/AUCINF.

The area under the first moment curve extrapolated to infinity (AUMCINF) was calculated by AUMCINF = AUMClast + \( t_{last} \times C_{last}/y + C_{last} \sqrt{y} \).

The volume of distribution (Vd) was not included because the actual Vd cannot be calculated correctly because the bioavailability is not known.

Statistical Evaluation. Statistical evaluation was performed with the statistical program SPSS 7.0. Direct comparison of the raw data was performed using the two-tailed paired t test. To evaluate a food effect, the data were log transformed and evaluated using the Wilcoxon test. According to Food and Drug Administration guidelines (18), there is no statistically significant food effect when the 90% confidence interval for the ratio fed and fasted treatment falls within 70–143% for the Cmax (log-transformed data) and 80–125% for the AUC (log-transformed data).

RESULTS

Safety/Efficacy. The safety of S-1 at the applied dose has been described previously (12). Because S-1 was administered only once without food and treatment was continued using the administration after food intake, no information is available on safety of drug intake without food.

Most patients consumed most of the breakfast that varied between 535 and 885 kcal. To determine whether a possible food-intake effect was related to the sequence of drug administration, differences in PK parameters between patients were evaluated by separate groups (arm A and B) and using pooled data.

Evaluation of Tmax and Vmax. The parent compound, FT, reached its Tmax earlier without breakfast (Fig. 1 and Table 2). This was observed in both arms of the study (\( P \leq 0.001 \)). The Cmax was significantly higher in the arm without breakfast as well.

The Tmax of 5FU was reached earlier without breakfast in both groups (\( P \leq 0.049 \)), with a significantly higher Cmax. The Tmax of CDHP was also reached earlier (\( P \leq 0.006 \)), whereas the Cmax was significantly higher in patients without breakfast.

The concentrations of the natural metabolite uracil were measured to evaluate the efficacy of DPD inhibition because

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**Table 1 Patient characteristics**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Female</th>
<th>Male</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal adenocarcinoma</td>
<td>7</td>
<td>10</td>
<td>7 (35–66)</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>3</td>
<td>10</td>
<td>7 (35–66)</td>
</tr>
<tr>
<td>Gastric carcinoma</td>
<td>3</td>
<td>5</td>
<td>7 (35–66)</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>2</td>
<td>5</td>
<td>7 (35–66)</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>1</td>
<td>2</td>
<td>7 (35–66)</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>1</td>
<td>2</td>
<td>7 (35–66)</td>
</tr>
<tr>
<td>Pancreas adenocarcinoma</td>
<td>1</td>
<td>2</td>
<td>7 (35–66)</td>
</tr>
</tbody>
</table>

found for the other metabolites (16), indicating no significant food effect. Both in experimental studies in Europe and North America and for registered use in Japan, S-1 is administered within 1 h after a meal twice daily. Because S-1 contains several compounds that are potentially acid-labile such as oxonic acid, food intake may potentially affect S-1 pharmacokinetics. The objective of this study was to evaluate the effect of food intake on the bioavailability of S-1 constituents.

**PATIENTS AND METHODS**

**Patients and Study Design.** A total of 18 patients was entered in this pharmacokinetic study after written informed consent was obtained. Table 1 summarizes the characteristics of these patients. All patients had an advanced cancer but with a good performance status.

All patients were randomized to two arms of the study and received S-1 at 35 mg/m\(^2\): in sequence A on day –7 without breakfast and on day 0 after breakfast; and in sequence B, at day –7 after breakfast and on day 0 without breakfast. The breakfast consisted of two slices of toast (one white, one whole wheat), two eggs cooked in butter (fried), one slice of ham, one slice of young Dutch cheese (or twice the sandwich filling of peanut butter or Nutella), 2 × 10 g of butter, 300 ml of whole milk, one glass of orange juice, and one cup of tea or coffee with sugar.

Blood was sampled 24 h before and at 30 min, 1 h, 2 h, 4 h, 8 h, 10 h, and 24 h after S-1 intake by venipuncture in heparinized tubes of 9 ml and transported on ice for immediate processing. Blood samples were centrifuged for 5 min at 4000 rpm and 4°C. The plasma was transferred to two Eppendorf vials of 2 ml and stored at −20°C. The extraction of plasma samples for FT, 5FU, oxonic acid, CDHP, and uracil analysis has been described previously (17). After extraction, the samples were stored at −20°C until analysis. Analysis for FT and cyanuric acid was performed by validated high-performance liquid chromatography assays, whereas the analysis of the other compounds was performed after derivatization by validated gas chromatography-mass spectrometry methods as described previously (17).

**Pharmacokinetic Evaluation.** The pharmacokinetic (PK) parameters for FT, 5FU, oxonic acid, cyanuric acid, CDHP, and uracil were calculated with the computer program WinNonLin (version 1.5). The data were analyzed using non-compartment analysis. The parameters that could be established

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plasma uracil is inversely related to DPD inhibition (19). Its natural concentrations are very low (<0.2 μM). Differences in uracil pharmacokinetics possibly reflecting variations in DPD inhibition were generally smaller than 5FU and CDHP. Only the corresponding Cmax of uracil was significantly higher in fasting patients ($P \leq 0.012$).

Because oxonic acid is an acid-labile compound, we expected to see pronounced variations and consequently accumulation of its catabolite cyanuric acid. The Tmax of oxonic acid was reached significantly faster in patients receiving no breakfast, with a significantly higher Cmax ($P \leq 0.007$). Cyanuric acid was not measurable in 7 fasting patients. In the remaining patients, the Tmax of cyanuric acid was lower in fasting patients (Tables 2, 3).

**Exposure.** There were no significant differences for the $T_{1/2}$, MRT, and AUC of FT when comparing the food with fasted arm (Table 2). Although the AUC for 5FU tended to be somewhat higher and the MRT was significantly lower in patients without breakfast ($P \leq 0.006$), the $T_{1/2}$ of 5FU were comparable. The AUC of CDHP was higher in patients without breakfast. The MRT and $T_{1/2}$ of uracil were not significantly different. Without breakfast, the AUC was significantly lower than with breakfast ($P \leq 0.025$).

The $T_{1/2}$ and MRT of oxonic acid were not significantly

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**Fig. 1** Concentration-time curves of S-1 after food and fasting. A representative curve of one patient is shown. ○ represents drug concentrations in fasting patients and ● from patients receiving S-1 after food intake.
different, but without breakfast, the AUC was significantly higher than with breakfast \((P < 0.025)\).

The \(T_{1/2}\) of cyanuric acid was not significantly different in both sequences, but the AUC was higher after breakfast compared with fasting, whereas in 7 patients, no AUC could be calculated. The MRT was higher in the other patients receiving breakfast in both sequences and was significantly different \((P < 0.026)\).

**Food Effect.** To evaluate the food effect according to the Food and Drug Administration criteria for a food effect, the data were log-transformed and evaluated with the Wilcoxon test (Ref. 18; Table 3). The 90% confidence intervals of the log-transformed Cmax of FT, 5FU, CDHP, and uracil were within 70–143% of the mean. The 90% confidence intervals of the log-transformed AUC of FT, 5FU, CDHP, and uracil were within 80–125% of the mean. However, oxonic acid and cyanuric acid were just outside this range.

**DISCUSSION**

Coadministration of food with S-1 affected the pharmacokinetics of some of the S-1 constituents, e.g., the rate but not the extent of FT and CDHP absorption were influenced. Because toxicity of S-1 is related to the AUC of 5FU \((12)\) and because the bioavailability of 5FU is within the Food and Drug Administration confidence intervals, it is unlikely that safety of S-1 will be affected by food. Food did not affect the AUC of CDHP. Similarly the accumulation of uracil, an indirect result of DPD inhibition, was only marginally affected. However, oxonic acid added to inhibit phosphoribosylation of 5FU to its active metabolite fluorouridine monophosphate, specifically in gut mucosa, showed a greater degradation in the food arm. This indicates that it might accumulate to a lesser extent in the gut mucosa, preventing to exert its protective effect.

Previous studies with oral fluoropyrimidine formulations reported an increase in the time period for absorption when food was given. Noncompartmental methods focusing on Cmax, Tmax, and AUC were used in these \((15, 16)\) and our study. For capecitabine \((16)\), the prodrug itself and its first metabolite showed a clear difference between the fed and fasting patients, but 5FU was only affected marginally. In the EU-5FU formulation, food decreased 5FU absorption possibly because 5FU itself was administered \((15)\). Irreversible suicide inactivation of

### Table 2: Pharmacokinetic parameters of S-1 after food and fasting

<table>
<thead>
<tr>
<th></th>
<th>FT</th>
<th>5FU</th>
<th>CDHP</th>
<th>Uracil</th>
<th>Oxonic acid</th>
<th>Cyanuric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (min)</td>
<td>Food</td>
<td>128</td>
<td>175</td>
<td>129</td>
<td>258</td>
<td>146</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>38(^b)</td>
<td>107(^c)</td>
<td>65(^d)</td>
<td>325</td>
<td>108(^e)</td>
</tr>
<tr>
<td>(CV%)</td>
<td>Food</td>
<td>38.7</td>
<td>33.1</td>
<td>34.9</td>
<td>34.9</td>
<td>4171</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>29.4</td>
<td>37.7</td>
<td>37.7</td>
<td>35.7</td>
<td>3926</td>
</tr>
<tr>
<td>Cmax (µM)</td>
<td>Food</td>
<td>7.97</td>
<td>13.0(^e)</td>
<td>1.46</td>
<td>2.48</td>
<td>5.56</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>1.60(^c)</td>
<td>3.27(^e)</td>
<td>4.99(^e)</td>
<td>8.5(^e)</td>
<td>1.29</td>
</tr>
<tr>
<td>AUC (µM × min)</td>
<td>Food</td>
<td>24.3 (\pm 3.84)</td>
<td>52.7 (\pm 24.3)</td>
<td>72.7 (\pm 26.9)</td>
<td>16.9 (\pm 18.4)</td>
<td>24.7 (\pm 2.97)</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>9.27</td>
<td>26.9</td>
<td>18.4</td>
<td>45.8</td>
<td>32.2(^f)</td>
</tr>
<tr>
<td>(CV%)</td>
<td>Food</td>
<td>28.3</td>
<td>24.7</td>
<td>24.7</td>
<td>32.4</td>
<td>32.4</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>24.4</td>
<td>24.4</td>
<td>24.4</td>
<td>32.4</td>
<td>32.4</td>
</tr>
<tr>
<td>T(_{1/2}) (min)</td>
<td>Food</td>
<td>41.1</td>
<td>28.7</td>
<td>28.3</td>
<td>26.3</td>
<td>63.1</td>
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<tr>
<td></td>
<td>Fast</td>
<td>24.7</td>
<td>24.4</td>
<td>24.4</td>
<td>23.2</td>
<td>73.2</td>
</tr>
<tr>
<td>(CV%)</td>
<td>Food</td>
<td>28.3</td>
<td>28.3</td>
<td>28.3</td>
<td>28.3</td>
<td>28.3</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>24.4</td>
<td>24.4</td>
<td>24.4</td>
<td>23.2</td>
<td>73.2</td>
</tr>
<tr>
<td>MRT (min)</td>
<td>Food</td>
<td>506</td>
<td>129</td>
<td>255</td>
<td>284</td>
<td>240</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>508</td>
<td>104</td>
<td>240</td>
<td>303</td>
<td>215</td>
</tr>
<tr>
<td>(CV%)</td>
<td>Food</td>
<td>33.0</td>
<td>20.9</td>
<td>28.2</td>
<td>35.9</td>
<td>38.6(^e)</td>
</tr>
<tr>
<td></td>
<td>Fast</td>
<td>30.6</td>
<td>30.6</td>
<td>30.6</td>
<td>39.8</td>
<td>47.0(^e)</td>
</tr>
</tbody>
</table>

\(^a\) Values are means of 18 patients with the CV as percentage (%). For cyanuric acid, the concentrations were too low in 7 patients receiving S-1 without breakfast.

\(^b\) FT, Ftorafur; 5FU, 5-fluorouracil; CDHP, 5-chloro-2,4-dihydroxypyridine; Tmax, time point of maximum observed concentration in plasma; CV, coefficient of variation; Cmax, concentration in plasma corresponding to Tmax; AUC, area under the plasma concentration-time curve; T\(_{1/2}\), terminal half-life; MRT, mean residence time.

\(^c\) Noncompartmental methods focusing on Cmax, Tmax, and AUC were used in these \((15, 16)\) and our study.

### Table 3: Food/Fast ratios of pharmacokinetic parameters

<table>
<thead>
<tr>
<th></th>
<th>Tmax(^b,c)</th>
<th>Cmax</th>
<th>AUC</th>
<th>Log-Cmax</th>
<th>Log-AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Food/Fast ((P))</td>
<td>Food/Fast (90% CI)</td>
<td>Food/Fast (90% CI)</td>
<td>Food/Fast (90% CI)</td>
<td>Food/Fast (90% CI)</td>
</tr>
<tr>
<td>FT</td>
<td>3.68 (0.000)</td>
<td>0.68 (0.57–0.80)</td>
<td>1.00 (0.88–1.13)</td>
<td>0.83 (0.77–0.89)</td>
<td>1.00 (0.98–1.01)</td>
</tr>
<tr>
<td>5FU</td>
<td>1.96 (0.005)</td>
<td>0.96 (0.69–1.24)</td>
<td>0.84 (0.76–0.92)</td>
<td>0.98 (0.95–1.00)</td>
<td>0.97 (0.95–0.98)</td>
</tr>
<tr>
<td>CDHP</td>
<td>2.06 (0.001)</td>
<td>0.84 (0.56–1.12)</td>
<td>0.89 (0.78–0.99)</td>
<td>0.95 (0.92–0.98)</td>
<td>0.98 (0.96–0.99)</td>
</tr>
<tr>
<td>Uracil</td>
<td>1.26 (0.069)</td>
<td>0.90 (0.87–0.93)</td>
<td>0.90 (0.86–0.94)</td>
<td>0.94 (0.92–0.96)</td>
<td>0.99 (0.98–0.99)</td>
</tr>
<tr>
<td>Oxonic acid</td>
<td>1.52 (0.003)</td>
<td>0.45 (0.35–0.55)</td>
<td>0.48 (0.36–0.61)</td>
<td>0.86 (0.83–0.90)</td>
<td>0.83 (0.79–0.88)</td>
</tr>
<tr>
<td>Cyanuric acid</td>
<td>2.45 (0.009)</td>
<td>2.45 (1.56–3.34)</td>
<td>5.08 (2.47–7.69)</td>
<td>1.09 (1.03–1.15)</td>
<td>1.23 (1.13–1.33)</td>
</tr>
</tbody>
</table>

\(^a\) The ratios for Cmax and AUC were calculated for each patient separately; the values given are the means of this ratio. For 5FU, CDHP, and uracil, the ratio could not be calculated for 1 patient, whereas for 7 patients, no ratio could be calculated for cyanuric acid because it was not detectable in the patients receiving no breakfast. The ratios for Cmax and AUC were also calculated for log-transformed data, which were subsequently also used to calculate the 90% CI.

\(^b\) FT, time point of maximum observed concentration in plasma; Cmax, concentration in plasma corresponding to Tmax; AUC, area under the plasma concentration-time curve; CI, confidence interval; FT, Ftorafur; 5FU, 5-fluorouracil; CDHP, 5-chloro-2,4-dihydroxypyridine.

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DPD prevents any degradation of 5FU, which is the major elimination pathway of 5FU. Without EU, the $K_m$ for elimination of 5FU equals the $K_m$ of 5FU for DPD (20), but with EU, this $K_m$ could not be calculated, and elimination did not follow Michaelis-Menten kinetics anymore, leaving a linear component. With S-1, which contains a reversible DPD inhibitor, elimination of 5FU is still biphasic, meaning that degradation still contributes to 5FU’s elimination, independent of food status.

The bioavailability of the other S-1 constituents has not been described earlier. Because CDHP is not metabolized, its elimination will be urinary excretion (17, 21). In experimental renal failure models, plasma clearance of CDHP was retarded (22) in line with the degree of renal impairment. Also, in patients with renal dysfunction, CDHP clearance was prolonged, leading to delayed $T_{1/2}$ and higher AUC of 5FU (22), possibly due to a retained DPD inhibition after a prolonged exposure.

In European and United States studies, diarrhea was the dose-limiting toxicity in contrast to Japan, where the formulation is registered and in clinical use with a similar efficacy compared with other oral formulations. Current clinical studies in the United States and Europe focus on a decrease of this diarrhea by either using another schedule such as a 2-weekly schedule because diarrhea mostly occurs in the last period of administration. Gastrointestinal side effects of S-1 are less common in Japanese patients (21, 23) compared with Europeans (12, 24). This might be due to potential ethnic and cultural differences such as food. Food had a profound effect on the bioavailability of oxonic acid, possibly because of its instability under acidic conditions and leading to a rapid increase in the concentration of cyanuric acid. This might reduce its anticipated protection against gastrointestinal side effects of 5FU because oxonic acid accumulates specifically in normal gut cells (25) to prevent 5FU metabolism to toxic metabolites. Considering the relatively heavy breakfast, protection under these circumstances might be limited. Future development of S-1 should aim to decrease gastrointestinal side effects either by using different schedules or by controlling the stability of oxonic acid.

**REFERENCES**


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