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ORIGINAL ARTICLE

Effect of food and a proton pump inhibitor on the pharmacokinetics of S-1 following oral administration of S-1 in patients with advanced solid tumors

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Abstract
Purpose S-1 is a novel oral fluoropyrimidine comprised of FT and two modulators, gimeracil (CDHP) and oteracil potassium (Oxo). This study investigated the food effects on the pharmacokinetics (PK) of Oxo, other components of S-1, and their metabolites at different gastric pH adjusted by proton pump inhibitor (PPI).
Methods Patients with and without PPI were treated with S-1 at 30 mg/m^2 twice daily orally on days 1–7 under either fed or fasting condition, and then were crossed over to fasting/fed conditions on days 15–21 with washout on days 8–14 and 22–28.
Results The study enrolled 55 patients including 27 PK-evaluable patients. For the single-dose and multiple-dose pharmacokinetics, the administration of S-1 under fed conditions resulted in decreased exposure to Oxo relative to fasting administration. There was a marginal decrease in exposure to CDHP and 5-FU under fed versus fasting conditions, although FT exposure was not altered by food, which demonstrated lack of food effect. PPI administration together with S-1 did not significantly change its bioavailability.
Conclusions Oxo exposure was reduced under fed compared to fasting condition. To increase the bioavailability of S-1, the administration of S-1 under fasting condition was more effective in the western countries.

Keywords Food effect · Phase I · Pharmacokinetics: advanced solid tumors · Fluoropyrimidines

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Introduction

S-1 is a new-generation oral fluoropyrimidine that combines tegafur (5-fluoro-1-(tetrahydro-2-furyl)uracil, FT), a prodrug of 5-fluorouracil (5-FU), with two modulators, gimeracil (CDHP, 5-chloro-2,4-dihydroxypyridine), which inhibits 5-FU degradation by inhibition of dihydropyrimidine dehydrogenase (DPD), and oteracil potassium (Oxo, monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6- carboxylate), which inhibits the phosphorylation of 5-FU in the digestive tract, in a molar ratio of 1:0.4:1 [1]. FT is a prodrug of 5-FU with excellent oral bioavailability (about 100%) [2]. It is gradually converted to 5-FU in vivo by CYP2A6 and exerts its antitumour activity by inhibiting DNA and RNA synthesis after being taken up by cancer cells (Fig. 1). When 5-FU is administered alone intravenously, 90% of the drug is rapidly catabolized in the liver by DPD and excreted in the urine as α-fluoro-β-alanine (FBAL) [3, 4]. CDHP inhibits the catabolism of 5-FU by reversible inhibition of DPD [5]. CDHP helps to maintain effective blood and tumor concentrations of 5-FU for a prolonged period; thus, potentially achieving a similar therapeutic effect as protracted infusion of 5-FU. 5-FU exerts its cytotoxicity after phosphorylation by orotate phosphoribosyltransferase (OPRT), which is inhibited by Oxo mainly in the gastrointestinal tract. Preclinical results

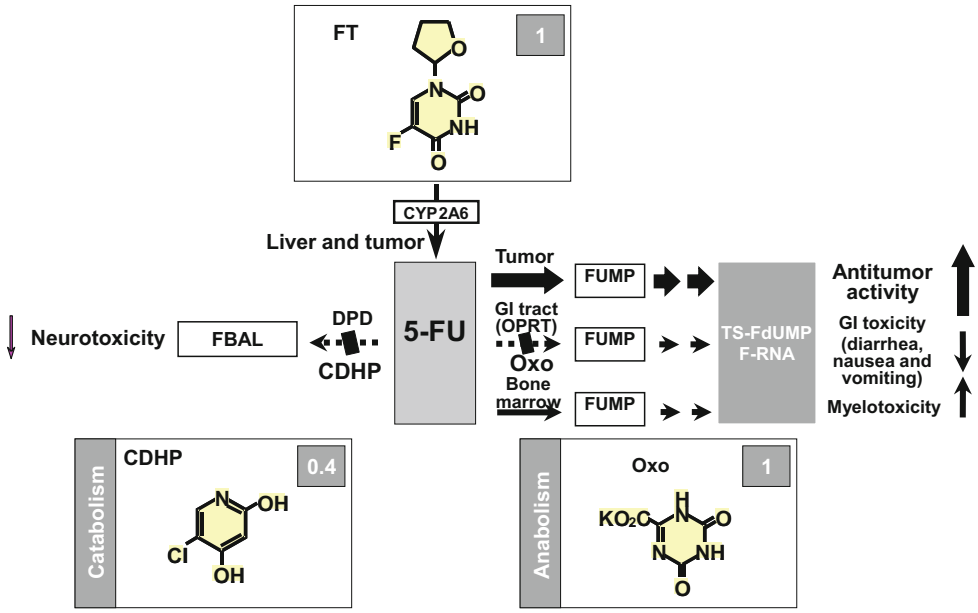

Fig. 1 Components of S-1 and its mechanism of action

have confirmed that the addition of Oxo to FT reduces the phosphorylation of 5-FU in normal gastrointestinal tract tissue, but not in tumor tissue due to its distribution in gastrointestinal tissues at high concentrations after oral administration, causing a decrease in gastrointestinal (GI) toxicity without affecting antitumor efficacy [6–9]. However, preclinical and clinical data also indicate that the Oxo is highly pH sensitive. Oral administration of S-1 to beagle dogs with predefined intragastric pH shows a 50% decrease in area under the plasma concentration–time curve (AUC) of Oxo at low intragastric pH compared with high intragastric pH. In addition, Oxo is stable at pH 5 ($t_{1/2}$ = 4.36 h) and unstable at pH 2 ($t_{1/2}$ = 0.94 h). The results of a previous food effect study suggested that the bioavailability of Oxo is greater when S-1 is administered under fasting conditions [10]. It is hypothesized that the effect of food on the bioavailability of Oxo is due to increased acid secretion in the stomach. If this is the case, the administration of an agent that raises intragastric pH, such as the proton pump inhibitor (PPI) pantoprazole sodium (pantoprazole), which decreases gastric acid secretion [11, 12], should improve the stability of Oxo in the stomach, thus increasing its bioavailability.

S-1 shows promising antitumor activity for several types of cancer in the large phase III studies conducted in Asia and western countries [13–17] and is currently approved for 7 tumor indications in Japan, 2 in Korea, and 1 in China and Singapore, and recently, 1 in Europe, respectively. However, the food effect on its pharmacokinetics (PK) was unknown.

The present study was designed to determine the effect of fed/fasting conditions on the pharmacokinetics (PK) of the components of S-1 (FT, CDHP, Oxo), 5-FU, FBAL, which are metabolites of FT and 5-FU, respectively, and uracil, and to determine the effect of the concomitant administration of a PPI on the PK of the components of S-1 and their metabolites administered under fed or fasting conditions.

Materials and methods

Study design and treatment

S-1 capsules were supplied by Taiho Pharma USA, Inc. (New Jersey, USA). Each capsule of S-1 contained 20 or 25 mg of FT. This was a multicenter, open-label, randomized study, in which patients were randomized in a 1:1:1:1 ratio to 1 of 2 study groups (Group A: S-1 administered concomitantly with a PPI; Group B: S-1 administered alone) and within each group to 1 of 2 sequences with respect to fed/fasting condition (fed condition followed by fasting condition or fasting condition followed by fed condition). All patients received S-1 30 mg/m^2 (as a dosage of FT) twice daily (bid) orally for two 7-day periods, except for days 1, 7, 15, and 21, when only 1 dose of S-1 was administered to allow for 24-hour PK analyses. During one of the 7-day treatment periods, S-1 was administered under fasting conditions, i.e., nothing by mouth (NPO) during the 2 h prior to and 2 h after S-1 administration; during the other 7-day treatment period, S-1 was administered under fed conditions, i.e., within 30 min after a standard breakfast (approximately 800–1,000 calories, consisting of 150 calories from protein, 250 calories from carbohydrate, and 500–600 calories from fat). The endpoint of the study was to investigate the clinical PK of the components of S-1 (FT, CDHP, Oxo) and their metabolites 5 FU, α-fluoro-β-alanine (FBAL), and uracil in patients with advanced-stage

solid tumors under fasting and fed conditions with or without a PPI and to investigate the safety and tolerability of S-1 administered in a BID oral dosing schedule.

All patients who completed the phase I (Cycle 1) cross-over part of the study had the option of continuing treatment in the phase II portion of study, in which patients received S-1 30 mg/m2 bid orally for 14 days following a 7-day recovery period, repeated every 21 days, until disease progression or any other reason for termination of S-1 treatment.

Patient eligibility

Patients with histologically or cytologically confirmed advanced or metastatic solid tumors without an option for established standard therapy were eligible. Patients may have received any number of prior therapies for advanced or metastatic disease. Patients had to be aged over 18 years. Other eligibility criteria were as follows: Karnofsky Performance Status (KPS) of 70–100%; absolute granulocyte count $\geq$1,500/μl; platelet count $\geq$100,000/μl; a hemoglobin value $\geq$9.0 g/dl; total bilirubin $\leq$1.5 times the upper limit of normal (ULN); transaminases AST and ALT $\leq$2.5 $\times$ ULN or AST and ALT may be $\leq$5 $\times$ ULN if related to underlying malignancy; and a serum creatinine $<$1.25 $\times$ ULN. Written informed consent was obtained from all patients. Patients were excluded if they had serious comorbidity that could interfere with protocol therapy or protocol compliance. Several other standard inclusion and exclusion criteria were implemented. The institutional review board for each participating institution approved the study protocol.

Pharmacokinetics

On days 1, 7, 15, and 21, blood was drawn predose (0 h) and at 0.5, 1, 2, 4, 6, 8, and 24 h after dosing. After immediate centrifugation, plasma was separated and stored in plain tubes at $-80°$ until analysis in a centralized laboratory. Plasma concentrations of analytes including FT, 5FU, CDHP, Oxo, and FBAL were measured by validated LC/MS/MS assay methods under Good Laboratory Practice conditions at Tandem Labs (West Trenton, NJ, USA). Pharmacokinetic parameters for each analyte were derived using WinNonlin Professional Version 5.0 or higher or SAS Version 9. The AUCs were calculated using noncompartmental methods. The actual time of the plasma sample relative to the dosing time was used to calculate the AUCs. In calculating the AUCs, a linear trapezoidal method was used for all portions of the plasma concentration–time curve.

For the test of the hypothesis, 2 distinct cross-over studies (Group A: S-1 + PPI; Group B: S-1 alone) were separately analyzed for the single-dose and the multiple-dose data. The primary PK parameters of interest were the $AUC_{0-\infty}$ (single dose only), AUC_{0-8h}, and C_{max} of FT, CDHP, Oxo, 5-FU, FBAL, and uracil. For each group (with and without a PPI), the effect of food on the PK of the components of S-1 and their metabolites was evaluated using a cross-over model with fixed effects for treatment (fasting or fed), sequence, and period and a random effect for patient within sequence. Ninety percent (90%) confidence intervals were constructed about the estimated treatment difference (fed–fasting). The test for sequence effect used the mean square for patients within sequence as the error term in constructing the F statistic. The data were log-transformed (base e) prior to analysis, and the confidence limits and point estimates obtained from the model were exponentiated after analysis such that the results are presented as ratios. In addition to

Table 1 Patient characteristics ($n = 27$)

Characteristics	*N*	%
Age, years		Min–Max
Median (range)	66.0	(28–81)
Gender		
Male	14	52
Female	13	48
Karnofsky performance status (KPS)		
100	15	56
90	5	19
80	6	22
Not done	1	4
Race		
Caucasian	27	100
BSA, m^2		
Median (range)	1.90	(1.44–2.66)
Tumor type		
Colorectal	7	26
Lung	4	15
Liver	2	7
Pancreas	2	7
Breast	2	7
Ocular melanoma	2	7
Unknown primary	2	7
Renal	1	4
Other	5	19
Prior surgery		
Resected	19	70
Not resected	8	30
Prior chemotherapy		
Yes	26	96
No	1	4
Prior radiotherapy		
Yes	11	41
No	16	59

Table 2 Single-dose plasma PK for FT, CDHP, Oxo, 5-FU, FBAL, and uracil

Analyte parameter	Study group		Geometric mean	*P* value[a]	Ratio of geometric means point estimate (90% CI)
FT					
$AUC_{0-\infty}$ (ng h/ml)	With PPI	Fed	15,186.42	0.7802	0.9848 (0.8953, 1.0834)
		Fasted	15,420.10		
	No PPI	Fed	14,963.77	0.1485	1.0764 (0.9886, 1.1719)
		Fasted	13,902.17		
	Contrast: PPI Fed versus No PPI Fasted			0.9548	1.0764 (0.9886, 1.1719)
C_{max} (ng/ml)	With PPI	Fed	1,152.16	<0.0001	0.6190 (0.5416, 0.7074)
		Fasted	1,861.31		
	No PPI	Fed	1,267.67	0.0036	0.7235 (0.6178, 0.8472)
		Fasted	1,752.21		
	Contrast: PPI Fed versus No PPI Fasted			<0.0001	0.6575 (0.5724, 0.7554)
t_{max} (h)	With PPI	Fed	Median	Min, Max	
		Fasted	2.93	0.52, 4.25	
			0.50	0.45, 1.08	
CDHP					
$AUC_{0-\infty}$ (ng h/ml)	With PPI	Fed	1,463.63	<0.0001	0.7211 (0.8953, 1.0834)
		Fasted	2,029.77		
	No PPI	Fed	1,370.64	0.0027	0.7497 (0.6555, 0.8575)
		Fasted	1,828.23		
	Contrast: PPI Fed versus No PPI Fasted			0.0007	0.8006 (0.7198, 0.8904)
C_{max} (ng/ml)	With PPI	Fed	182.70	<0.0001	0.4286 (0.3753, 0.4896)
		Fasted	426.23		
	No PPI	Fed	233.49	0.0004	0.5889 (0.4867, 0.7125)
		Fasted	396.49		
	Contrast: PPI Fed versus No PPI Fasted			<0.0001	0.64608 (0.3943, 0.5385)
t_{max} (h)	With PPI	Fed	Median	Min, Max	
		Fasted	2.03	1.10, 4.10	
			0.99	0.50, 1.13	
OXO					
$AUC_{0-\infty}$ (ng h/ml)	With PPI	Fed	241.91	0.0193	0.5305 (0.3500, 0.8042)
		Fasted	455.99		
	No PPI	Fed	147.44	0.0001	0.2904 (0.2033, 0.4147)
		Fasted	507.79		
	Contrast: PPI Fed versus No PPI Fasted			0.0008	0.4764 (0.3338, 0.0.6799)
C_{max} (ng/ml)	With PPI	Fed	27.99	<0.0001	0.4286 (0.3753, 0.4896)
		Fasted	71.72		
	No PPI	Fed	22.48	<0.0001	0.2645 (0.1906, 0.3670)
		Fasted	84.99		
	Contrast: PPI Fed versus No PPI Fasted			<0.0001	0.3293 (0.2502, 0.4334)
t_{max} (h)	With PPI	Fed	Median	Min, Max	
		Fasted	2.08	1.10, 8.12	
			2.00	0.50, 4.10	
5-FU					
$AUC_{0-\infty}$ (ng h/ml)	With PPI	Fed	616.27	<0.0001	0.7509 (0.6903, 0.8168)
		Fasted	820.75		
	No PPI	Fed	754.29	0.0037	0.8549 (0.7918, 0.9230)
		Fasted	882.36		
	Contrast: PPI Fed versus No PPI Fasted			<0.0001	0.6984 (0.6471, 0.7538)

Table 2 continued

Analyte parameter	Study group		Geometric mean	*P* value[a]	Ratio of geometric means point estimate (90% CI)
C_{max} (ng/ml)	With PPI	Fed	98.07	<0.0001	0.7160 (0.6468, 0.7926)
		Fasted	136.97		
	No PPI	Fed	133.47	0.0009	0.8385 (0.7815, 0.0.8997)
		Fasted	159.17		
	Contrast: PPI Fed versus No PPI Fasted			<0.0001	0.6161 (0.5671, 0.6694)
FBAL					
$AUC_{0-\infty}$ (ng h/ml)	With PPI	Fed	1,346.47	0.5256	0.7362 (0.2876, 1.8846)
		Fasted	1,828.91		
	No PPI	Fed	1,713.88	0.8620	0.9917 (0.8936, 1.1005)
		Fasted	1,728.29		
	Contrast: PPI Fed versus No PPI Fasted			0.2101	0.7791 (0.4532, 1.3392)
C_{max} (ng/ml)	With PPI	Fed	81.24	0.1743	0.8941 (0.7788, 1.0265)
		Fasted	90.85		
	No PPI	Fed	86.57	0.0106	0.8959 (0.8402, 0.9553)
		Fasted	96.63		
	Contrast: PPI Fed versus No PPI Fasted			0.0038	0.8407 (0.7591, 0.9311)
Uracil					
$AUC_{0-\infty}$ (ng h/ml)	With PPI	Fed	8,966.56	0.0025	0.5305 (0.3500, 0.8042)
		Fasted	11,202.19		
	No PPI	Fed	10,100.14	0.0649	0.2904 (0.2033, 0.4147)
		Fasted	10,854.24		
	Contrast: PPI Fed versus No PPI Fasted				
C_{max} (ng/ml)	With PPI	Fed	823.35	<0.0001	0.7623 (0.7185, 0.8089)
		Fasted	1,080.04		
	No PPI	Fed	908.74	0.0041	0.8627 (0.8017, 0.9284)
		Fasted	1,053.39		
	Contrast: PPI Fed versus No PPI Fasted			<0.001	0.7816 (0.7337, 0.8327)

PK data were analyzed for 27 patients

[a] *P* values: Wilcoxon signed rank test

these analyses, the contrast of (with PPI/fed) versus (without PPI/fasting) was constructed using the least-squares (LS) means, variance terms, and degrees of freedom from the respective analyses. The point estimate and the 90% confidence interval were constructed about the estimated treatment difference [(with PPI/fed)—(without PPI/fasting)]. These results were exponentiated in order to present them as ratios. A formal analysis comparing the PK of S-1 when administered with PPI to those when S-1 was administered alone was not performed.

Results

Patient demographics

Between May 2004 and September 2005, a total of 60 Caucasian patients were enrolled. Five patients did not receive study drugs because of progression of malignant disease (2 patients), withdrawal of consent, stable disease, and investigator judgment (1 patient, each). Thus, a total of 55 patients received study. The PK population comprised of 27 patients from the patients enrolled under protocol amendment. Forty-five patients (81.8%) entered the treatment continuation phase (phase II) of the study. The primary reason for discontinuing study medication (all cycles) was objective progression of malignant disease (43 patients, 78.2%). Table 1 shows the patient characteristics.

Pharmacokinetics

As shown in Table 2, an effect of food on the $AUC_{0-\infty}$ and C_{max} of Oxo was demonstrated when S-1 was administered alone (without PPI) or in combination with a PPI. The point estimates and 90% CI for the ratio of the geometric means (fed vs. fasted) for $AUC_{0-\infty}$ were 0.29 (CI 0.20–0.41) for

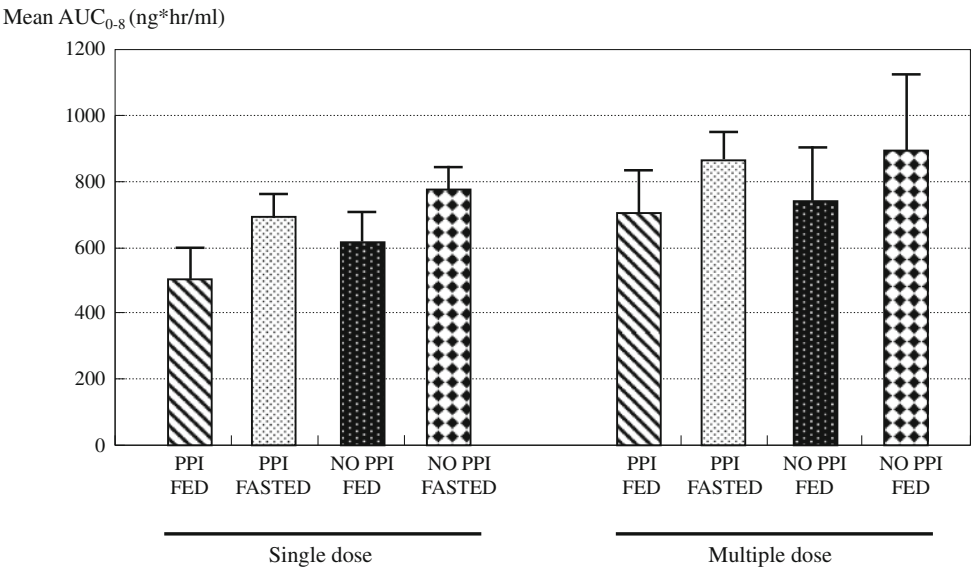

Fig. 2 Mean $AUC_{0\text{-}8h}$ of 5-FU by treatment group (PPI/No PPI) in fed and fasting condition after the administration of S-1 (30 mg/m^2). AUC, area under the plasma concentration–time curve. Standard error (SE) bars were given for each PK parameters

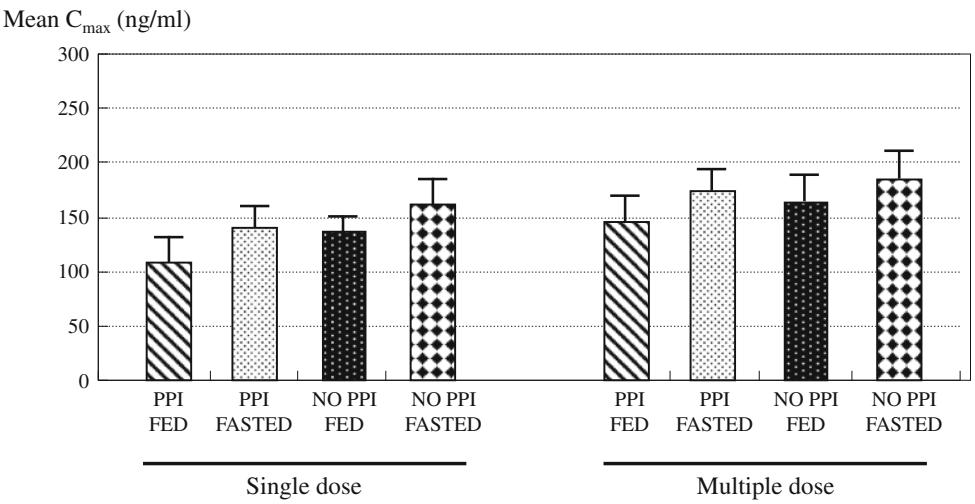

Fig. 3 Mean C_{max} of 5-FU by treatment group (PPI/No PPI) in fed and fasting condition after the administration of S-1 (30 mg/m^2). C_{max}, concentration in plasma corresponding to T_{max}

S-1 administered alone and 0.53 (CI 0.35–0.80) for S-1 administered with a PPI. The corresponding estimates for C_{max} were 0.26 (CI 0.19–0.37) for S-1 administered alone and 0.39 (CI 0.31–0.50) for S-1 administered with a PPI. The difference in the ratios for S-1 alone and that of S-1 plus PPI suggests that PPI blunts the effect of food on the PK of Oxo; i.e., there is an increase in the $AUC_{0-\infty}$ of Oxo under fed condition with concomitant PPI administration (geometric mean = 241.91 ng h/ml) compared to S-1 alone under fed condition (geometric mean = 147.44 ng h/ml), but not of sufficient magnitude to negate the food effect (geometric mean = 455.99 ng h/ml under fasting condition with PPI). Food had little impact on the median t_{max} for Oxo. It was approximately 2 h for both the fed and fasting condition regardless of presence or absence of a PPI. A food effect on the PK of CDHP was demonstrated when S-1 was administered with a PPI. The point estimates and 90% CI for the ratio of the geometric means (fed vs. fasted) for $AUC_{0-\infty}$ were 0.72 (CI 0.66–0.78). When S-1 was administered alone, the effect of food on the $AUC_{0-\infty}$ was indeterminate; the point estimate and 90% CI were 0.75 (CI 0.66–0.86), i.e., the 90% confidence limits for the ratio of geometric means overlap the boundaries that define bioequivalence (0.80–1.25). Even though the food effect is indeterminate, the results suggest that exposure to CDHP is substantially diminished when S-1 alone is administered under fed conditions. Administering S-1 with food slightly increased the median t_{max} for CDHP. Regardless of treatment with or without a PPI, the median t_{max} was approximately 1 h under fasting conditions and 2 h under the fed condition. There was no observed food effect on the $AUC_{0-\infty}$ of FT either when S-1 was administered alone (without PPI) or in combination with a PPI with point estimates and 90% CI of 1.1 (CI 0.99–1.17) and

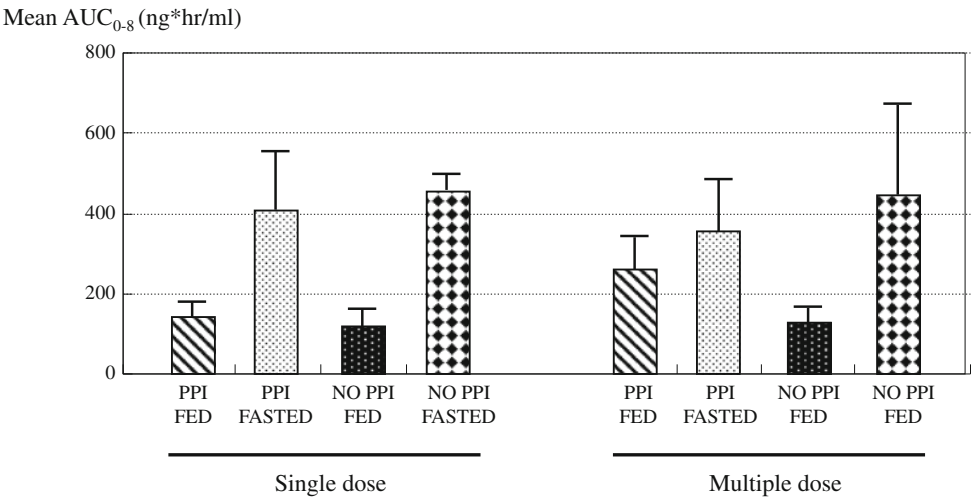

Fig. 4 Mean $AUC_{0\text{-}8h}$ of Oxo by treatment group (PPI/No PPI) in fed and fasting condition after the administration of S-1 (30 mg/m^2)

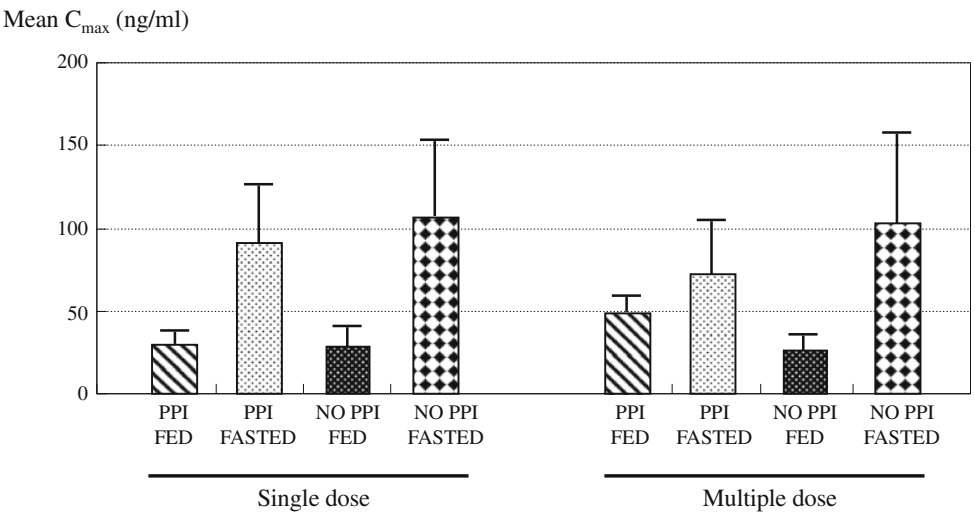

Fig. 5 Mean C_{max} of Oxo by treatment group (PPI/No PPI) in fed and fasting condition after the administration of S-1 (30 mg/m^2)

0.98 (CI 0.90–1.08), respectively. Food appeared to delay the attainment of the t_{max} of FT. Regardless of treatment with or without a PPI, the median t_{max} was approximately 0.5 h under fasting conditions and 2–3 h under the fed condition. The results obtained for the single-dose and multiple-dose pharmacokinetics were qualitatively similar. The results for single-dose and multiple-dose $AUC_{0\text{–}8h}$ and C_{max} for 5-FU and Oxo are displayed graphically, because there were significant differences in fed in fed versus fasting condition for $AUC_{0\text{–}8h}$ and C_{max} of these analytes. AUC and C_{max} of CDHP were not shown, because they were correlated with the 5-FU's (Figs. 2, 3, 4, 5).

Discussion

This study was primarily designed to assess the PK of the components of S-1 (FT, CDHP, Oxo) and their metabolites in patients with advanced-stage solid tumors under fasting and fed conditions with or without a proton pump inhibitor. Under fed conditions, the $AUC_{0\text{–}\infty}$ and C_{max} of Oxo were significantly reduced compared to that observed under fasting conditions (without PPI). When S-1 was administered in combination with pantoprazole, the difference in exposure (fed vs. fasted) of Oxo was diminished, but a significant food effect was still observed. The reason for the observed difference in Oxo PK irrespective of PPI administration is not clear, but the difference of gastric emptying rate (GER) could have affected the PK of Oxo. The exposure to CDHP was also reduced when S-1 was administered under fed conditions with or without concomitant PPI administration. When S-1 was administered alone (without PPI) under the fed condition, there was a decrease in the $AUC_{0\text{–}\infty}$ and C_{max} of 5-FU of 15 and 16% respectively, compared with the fasting condition. Concomitant administration of S-1 and a PPI under the fed condition also resulted in a decrease in the $AUC_{0\text{–}\infty}$ and C_{max} of 5 FU (25 and 28% respectively) compared

with the fasting condition. The decrease in 5-FU exposure under fed conditions may be linked to the reduction in CDHP exposure that was observed in this study. Hirata et al. [18] stated that C_{max} and AUC of S-1 correspond to that of 5-FU administered at 300 mg/m^2/day. However, the ratio of duration, in which the 5-FU plasma level is within a certain range (e.g., 50–200 ng/ml), is higher for S-1 in comparison with other drugs, when consecutive oral administration was used, and the combination of CDHP and FT was successful to allow an effect similar to that of long-term 5-FU/CVI treatment to be obtained. In addition, the population pharmacokinetic analysis of the several clinical studies of S-1, including the present study, revealed that when patients took S-1 with a meal, C_{max} of all analytes tended to apparently decrease due the delayed absorption, and bioavailability of Oxo apparently decreased to 31.6% [19]. However, the expected decrease in 5-FU AUC is limited to approximately 14%. Therefore, although food affects the Oxo AUC and may impact the incidence of GI toxicities, the observed difference of 5-FU AUC after the administration of S-1 in the fed versus fasting condition seems to be too small to affect the pharmacodynamics (efficacy/safety) of 5-FU. These findings are consistent with the report by Peters et al. [20] On the other hand, food did not significantly affect the $AUC_{0-\infty}$ of FBAL and uracil when S-1 was administered alone or concomitantly with a PPI.

The results of the clinical studies have shown that GI toxicities of S-1 were mild. In the large phase III study conducted in USA and EU[14], the rates of grade 3 or more diarrhea, stomatitis, and vomiting were less than 5% when S-1 was administered with the fasting condition in combination with cisplatin, which seems to prove the protective role for GI tract by Oxo.

Recently, S-1 was approved in Europe for the advanced gastric cancer. Because the results of our study suggest that S-1 should be administered without food in the western population, it is recommended that S-1 be administered without food in Europe.

In comparison, a food effect on the PK of capecitabine and its metabolites was observed as well. However, capecitabine was to be administered with food at present, because this procedure was used in the clinical trials [21].

In conclusion, the administration of S-1 with a standard high-fat and high-calorie meal reduces exposure to Oxo, CDHP, and 5-FU with a more pronounced effect for Oxo. This decrease in exposure is somewhat blunted by concomitant administration of a PPI, but not of sufficient magnitude to negate the food effect. The administration of S-1 under fasting condition was more effective to increase the bioavailability of Oxo.

Conflict of interest KS and CZ are employees of Taiho Pharma, USA, Inc. No other potential conflict of interest relevant to this article was reported.

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