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ORIGINAL ARTICLE

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Estimation of the effect of food on the disposition of oral 5-fluorouracil in combination with eniluracil

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Abstract *Aims:* To determine the effect of food on the pharmacokinetics of 5-fluoruracil (5-FU) taken orally with eniluracil and to compare the performance of different pharmacokinetic analysis methods in the detection a potential food-drug interaction. *Methods:* In a randomized, open-label, two-way crossover study, 12 patients received eniluracil (50 mg, orally) on days 1 and 2 and 5-FU (20 mg/m^2, orally) on day 2 following either a 2-h fast or 20 min after a standard meal. Treatments were separated by 7 days. Timed blood samples were collected during the first two treatment periods and 5-FU concentrations determined by GC/MS. Data were analyzed and pharmacokinetic parameter estimates were obtained using a noncompartmental, two-stage and population analysis methods. *Results:* In fasted individuals, the clearance/bioavailability of 5-FU was estimated to be 5.6 l/h. The mean absorption lag-time was 0.24 h and was followed by rapid absorption of 5-FU. Administration of 5-FU and eniluracil with food resulted in a decrease in the 5-FU absorption rate constant by 90%. As a result, the peak plasma concentration (C_{max}) of 5-FU was decreased by 21% and the time to C_{max} was increased 2.9-fold. Clearance of 5-FU, relative bioavailability, and area under the plasma concentration vs time curve (AUC) remained unchanged with coadministration of food. Similar results were obtained using all three data analysis methods. *Conclusions:* Administration of food with oral 5-FU and eniluracil slowed absorption of 5-FU and decreased 5-FU C_{max}, but did not effect AUC. Further investigation of the incorporation of population pharmacokinetic approaches in food effect studies is warranted.

Keywords 5-Fluorouracil · Eniluracil · Food-drug interaction · Pharmacokinetic analysis

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Introduction

5-Flurouracil (5-FU) was first synthesized in 1957 as an antimetabolite for the treatment of cancer [1]. It is currently approved in the United States for treatment of colorectal, stomach, breast, and pancreatic cancers. 5-FU is a prodrug that is activated by a series of anabolic reactions to 5-fluoro-2′-deoxyuridine monophosphate (FdUMP) which binds to and inactivates thymidylate synthase [2]. Additionally, anabolites of 5-FU are incorporated into both DNA and RNA, causing replication, transcription, and translation errors that result in cell toxicity [3, 4]. However, the efficacy of 5-FU is limited by rapid catabolic metabolism in the liver and tissues to 5,6-dihydro-5-fluorouracil (FUH_2) by the rate-limiting enzyme dihydropyrimidine dehydrogenase (DPD). 5-FU administered orally is poorly absorbed with bioavailability ranging from 0 to 80% due to rapid first-pass metabolism by DPD in the intestine and liver [5]. Since there is some evidence that 5-FU AUC (area under the plasma concentration versus time curve) correlates with toxicity and tumor response, variability in the bioavailability of 5-FU may result in unpredictable toxicities and responses [6, 7].

There are many potential clinical advantages to modulating DPD activity. These include decreasing interpatient variability in drug exposure caused by variability in DPD activity due either to polymorphic enzyme expression or circadian variations in DPD activity [8]. Standard doses of 5-FU in the face of

homozygous deletion of the DPD gene results in severe neurotoxicity, myelosuppression, and gastrointestinal toxicities [9, 10, 11], implicating DPD as an essential enzyme in the catabolism of 5-FU. The efficacy of 5-FU correlates with the expression and activity of DPD in tumors and inactivation of DPD may improve its efficacy [12, 13].

Eniluracil, an ethynyl derivative of uracil, is an irreversible, mechanism-based inactivator of DPD [14, 15, 16, 17]. Eniluracil alone does not have antiproliferative activity, but increases the cytotoxicity of 5-FU in vitro [18] and improves the efficacy of 5-FU in animal models [17, 19]. DPD activity was completely inactivated in colorectal tumors resected from patients receiving eniluracil for 3 days [20]. In addition, inactivation of DPD by eniluracil allows effective oral administration of 5-FU with 100% bioavailability [21].

In previous phase I clinical trials of orally administered 5-FU and eniluracil, the pharmacokinetics were determined following a 2-h fast [16, 21]. The purpose of this open label, randomized, two-way crossover study was to determine the effect of a standard meal on the absorption, disposition, and elimination of oral 5-FU in the presence of DPD inhibition by eniluracil.

Population pharmacokinetic models are sometimes used to determine bioequivalence and may be used to determine food effects on the absorption, distribution and elimination of orally administered drug [22, 23]. More commonly, two-stage compartmental analysis or noncompartmental methods are used to determine these effects. Therefore, a secondary objective was to compare a population pharmacokinetic analysis to the traditional two-stage estimation or noncompartmental methods for describing the effects of food on the pharmacokinetics of 5-FU administered orally with eniluracil. Use of population models allows estimation of the magnitudes of inter- and intraindividual variability while simultaneously determining the influence of food on 5-FU pharmacokinetics.

Methods

Patient population

The 12 patients enrolled in this study were required to have a histologically confirmed solid tumor malignancy that was refractory to standard therapy or for which no standard therapy was available, a life expectancy greater than 12 weeks, and to be older than 18 years. Informed written consent was obtained from all patients in accordance with institutional and federal guidelines. Patients were required to have a Karnofsky performance status of at least 70%, platelets $>120{,}000/mm^3$, hemoglobin >9 g/dl, granulocytes $>2000/mm^3$, total bilirubin <1.25 times normal, and an estimated creatinine clearance greater than 50 ml/min. Patients were not eligible for this study if they could not swallow and retain oral medication or if they had stomach or small bowel resections or active gastrointestinal tract diseases, including chronic diarrhea or malabsorption syndromes. Pregnant or lactating females were not eligible and all patients with reproductive potential were required to use effective contraceptive methods if sexually active. Patients were not allowed to have received any investigational drug in the previous 2 weeks, any chemotherapy in the previous 4 weeks, or either nitrosourea or mitomycin-C in the previous 6 weeks. Biological or hormonal therapy (except replacement) or radiation therapy was not allowed within 4 weeks of the study. Dipyridamole, trimethoprim, folinic acid, misonidazole, allopurinol, metoclopramide, cimetidine, and fluocytosine could interfere with the pharmacokinetics or pharmacodynamics of eniluracil and/or 5-FU, and were not allowed prior to or during the study.

Study design

Doses of 5-FU (20 mg/m^2) were based on body surface area calculated by the DuBois formula and rounded down to the nearest 5 mg. Patients received 50 mg eniluracil orally on days 1 and 2. They were randomized to receive 5-FU orally on day 2 following either a 2-h fast or 20 min after a standard high fat, high calorie meal consisting of two eggs, two strips of bacon, toast with butter, 113 g hash brown potatoes, and 228 g whole milk. Patients were allowed to drink water ad libitum with the meal. Following a 7-day washout period, patients received the other treatment schedule. Following a second 7-day washout period, patients received eniluracil orally on days 1–7 and 5-FU orally on days 2–6. This regimen of eniluracil on days 1–7 and 5-FU on days 2–6 was repeated every 4 weeks until disease progression or unacceptable toxicity.

Plasma sampling and assay methods

Blood samples (4 ml) were collected in 5 ml heparinized tubes prior to dosing and at 0.13, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 h following 5-FU administration on day 2 of both treatment periods. Plasma was obtained by centrifugation at 4°C and frozen at –20°C until analysis. The concentration of 5-FU in plasma was analyzed by Triangle Laboratories (Durham, N.C.) using a validated gas chromatography/mass spectrometry (GC/MS) method as described previously [15, 16, 21]. Briefly, samples (0.5 ml) were extracted with three aliquots of isopropanol/ethyl acetate (50:50). The organic extracts were passed through sodium sulfate columns to remove water, then dried with nitrogen. Analytes were derivatized with *N*-methyl-*N*-(*t*-butyldimethylsilyl)trifluoroacetamide, then analyzed by GC/MS with selected ion monitoring. The range for the assay was 1 to 1000 ng/ml. Typical intra-assay precision and accuracy is 6.2–16.4% and 95.7–110.5%, respectively [15].

Pharmacokinetic analysis

Noncompartmental pharmacokinetics of 5-FU were determined using WinNonlin Pro, Version 1.5 (Scientific Consulting, Apex, N.C.). The following relationships were used to calculate the pharmacokinetic parameters. The $AUC_{0\text{-}\infty}$ (area under the plasma concentration time curve from time zero to infinity) was calculated using the log-linear trapezoidal rule from time zero to the time of the last plasma concentration (AUC_{last}) plus the last measurable concentration divided by the terminal elimination rate constant ($AUC_{last} + C_{last}/K_{el}$). The elimination rate constant (K_{el}) was calculated as the terminal slope of a semilogarithmic plot of the concentration versus time curve. The apparent clearance (CL/F) was calculated as dose/$AUC_{0\text{-}\infty}$. The apparent volume of distribution (V_d/F) was calculated as dose/$K_{el} \times AUC_{0\text{-}\infty}$. Maximal plasma concentration (C_{max}) and its associated time (T_{max}) were determined by inspection of the plasma concentration versus time curves. Subject-specific estimates of the relative bioavailability of 5-FU after food was estimated as the ratio AUC_{fed} to AUC_{fasted}.

One-compartment pharmacokinetic parameter estimates were determined by the traditional two-stage method using WinNonlin Standard, Version 1.1 (Scientific Consulting). Data for each subject from both the fed and fasted treatments were fitted to a one-compartment open model with first-order absorption and elimination and allowing for an absorption lag time. Estimated parameters of this model were V_d/F, K_{el}, the absorption rate

constant (K_a) and an absorption lag time (T_{lag}). Model-based estimates of 5-FU C_{max} and T_{max} were also obtained.

Population pharmacokinetic estimates were obtained using the first-order conditional estimation method in the NONMEM program (Version V, NONMEM Project Group, UCSF, San Francisco, Calif.) [24]. Typical values of K_a, T_{lag}, V_d/F and CL/F were estimated in the population analysis. Parameter estimates obtained by the two-stage method were used as initial estimates. Both additive and proportional error models were tested to describe interindividual variability in each parameter and to describe intraindividual variability. The effect of food on each parameter was examined sequentially using an indicator variable. For example:

$$K_a = \theta_1 \times (1 - Q) + \theta_2 \cdot Q \quad (1)$$

where Q is an indicator variable which has a value of 0 for fasted treatment and a value of 1 for fed treatment and θ_1 and θ_2 are parameters to be estimated, such that K_a equals θ_1 for fasted treatment and K_a equals θ_2 for fed treatment.

Table 1. Patient characteristics

Age (years)	
Median	60
Range	50–78
Weight (kg)	
Median	80
Range	46–117
Sex	3 male/9 female
Performance status (*n*)	
100	5
90	3
80	3
70	1
Prior treatment (*n*)	
Chemotherapy alone	4
Surgery alone	4
Radiation and chemotherapy	3
No therapy	4
Diagnosis (*n*)	
Colon	2
Ovarian	3
Rectal	1
Breast	1
Stomach	1
Gallbladder	1
Endometrial	1
Unknown primary	2

Statistics

Differences in 5-FU pharmacokinetics between the fasted and fed treatments were examined. Two-stage estimates of individual pharmacokinetic parameters for each of the two treatments were compared by paired Student's *t*-test using Stata (Stata Corporation, College Station, Tx.) or InStat (GraphPad Software, San Diego, Calif.). A *P*-value of 0.05 was considered significant for all comparisons. The distributions of all pharmacokinetic parameters about the mean were tested for normality by the Kolmogorov-Smirnov test using Instat with a significance level of $P = 0.05$.

In the population analysis, model selection was determined using the likelihood ratio test, using a change in objective function corresponding to a significance level of $P < 0.05$ [24]. Hence, a decrease in the objective function by four points was required for the effect of food on a parameter to be considered significant. All parameters found to be significantly influenced by food were included in the full model and the final model was obtained by stepwise deletions of these effects from the full model. The best model was selected by reduction in the objective function and examination of diagnostic plots.

Results

Patient characteristics

Patient characteristics are shown in Table 1. All received full doses as specified by the protocol for both periods one and two.

Pharmacokinetics of 5-FU

The noncompartmental pharmacokinetic parameters of 5-FU are shown in Table 2. The most significant find-

Table 2. Noncompartmental and two-stage estimates of the pharmacokinetics of 5-FU administered orally with eniluracil. Values are means ± SD (V_d/F apparent oral volume of distribution, K_{el} elimination rate constant, CL/F apparent clearance, K_a absorption rate constant, T_{lag} absorption lag time, T_{max} time of the maximal plasma concentration, C_{max} maximal plasma concentration, $AUC_{0\text{-}\infty}$ area under the plasma concentration vs time curve from time zero to infinity)

		Noncompartmental	Two-stage
V_d/F (l)	Fasting	45.3 ± 12.6	34.7 ± 9.2
	Fed	49.8 ± 17.3	36.1 ± 7.7
K_{el} (h^{-1})	Fasting	0.12 ± 0.03	0.18 ± 0.08
	Fed	0.12 ± 0.03	0.17 ± 0.06
CL/F (l/h)	Fasting	5.34 ± 1.91*	–
	Fed	5.65 ± 1.90	–
K_a (h^{-1})	Fasting	–	12.1 ± 10.1*
	Fed	–	3.4 ± 3.9
T_{lag} (h)	Fasting	–	0.27 ± 0.13*
	Fed	–	0.56 ± 0.47
T_{max} (h)	Fasting	0.80*[a]	0.82 ± 0.43*
	Fed	1.95	2.38 ± 1.70
C_{max} (μg/l)	Fasting	1092 ± 302*	1008 ± 195*
	Fed	822 ± 267	795 ± 235
$AUC_{0\text{-}\infty}$ (μg·h/l)	Fasting	7740 ± 2162*	7009 ± 2488
	Fed	7061 ± 2226	6596 ± 1988

*$P < 0.05$ (unpaired Student's *t*-test, except Wilcoxon Rank Sum test for T_{max} fasting median value)
[a]Median

ings were a 25% reduction in the C_{max} of 5-FU with a 2.4-fold increase in the T_{max} when 5-FU was taken with food. There was an increase in CL/F and decrease in AUC following administration of 5-FU with a meal. However, these changes, although statistically significant were modest (6% increase and 9% decrease, respectively). The relative bioavailability of 5-FU in the presence of food, as calculated by the ratio of AUC_{fed} to $AUC_{fasting}$, was estimated to be 0.97 (95% confidence interval 0.86–1.06).

The pharmacokinetic parameters of 5-FU determined by the two-stage estimation method are summarized in Table 2. Administration of eniluracil and 5-FU to patients following a meal resulted in a 2.9-fold increase in T_{max}, and a 21% decrease in C_{max}. This was accompanied by a significant delay in absorption of 5-FU, as seen by the 2-fold increase in absorption lag time. With the one-compartment estimation of parameters, the clearance of 5-FU was not affected by the presence of food. Further, there was no change in drug exposure as shown by an equivalent AUC for each treatment period, which was confirmed by a modest change in the relative bioavailability. Interpatient variability in K_a, T_{lag}, T_{max} and C_{max} was increased when subjects were fed prior to drug administration.

A one-compartment model with first-order absorption, an absorption lag period and an additive residual error model provided the best fit to the data. The effect of food on each pharmacokinetic parameter was evaluated. In the initial screening, there was a significant effect of food on K_a and T_{lag}. There was little effect on F, as shown by little change in the objective function when a food effect was included on either CL/F or V_d/F. The incorporation of a food effect on K_a yielded a drop in the objective function of 540 for the addition of a single parameter. There was no additional change in the objective function when a food effect was incorporated for T_{lag}. The best fit to the data was a model parameterized in CL/F, V_d/F and T_{lag}, and with different estimates of K_a for the fed and fasted groups. Parameter estimates are shown in Table 3.

Table 3. Population estimates of the pharmacokinetics of 5-FU administered orally with eniluracil. Values are means ± SE (*CL/F* apparent clearance, V_d/F apparent volume of distribution, K_a absorption rate constant, T_{lag} absorption lag time)

CL/F (l/h)	5.6 ± 0.5
V_d/F (l)	33.5 ± 2.3
K_a (fasting) (h^{-1})	15.1 ± 7.0
K_a (fed) (h^{-1})	1.3 ± 0.5
T_{lag} (h)	0.24 ± 0.003
Interindividual variability (%CV)	
CL/F	30 ± 19%
V_d/F	24 ± 14%
K_a (fasting)	141 ± 72%
K_a (fed)	163 ± 101%
Intraindividual variability (μg/l)	72 ± 34

Discussion

In this study, the effects of food on the pharmacokinetics of orally administered 5-FU administered with eniluracil were determined. Coadministration of 5-FU and eniluracil orally with food decreased the rate but not the extent of 5-FU absorption. The absorption rate was decreased by more than 85% as estimated in the population analysis using NONMEM. It should be noted that the estimated effect on the absorption rate was only 70% using the traditional two-stage approach. As a result of the effect on K_a, there was a significant increase in T_{max} and decrease in C_{max}. However, there was no effect of food on the bioavailability and thus on the AUC. As the toxicity and efficacy are usually more closely related to AUC than peak concentration [6, 7], it is unlikely that this pharmacokinetic effect will be clinically significant.

The plasma concentrations of 5-FU in this study were fit to a one-compartment open model with first-order absorption and elimination rate constants and an absorption lag. In a study with interferon alfa-2a, an inhibitor of DPD [25], the pharmacokinetics of orally administered 5-FU, fitted a two-compartment model only when K12 was much greater than K21 or when a second linear elimination process was added. In the absence of interferon, clearance from the central compartment followed both first-order linear and Michaelis-Menten processes. The K_m for elimination of 5-FU for the route described by Michaelis-Menten kinetics was approximately equal to the K_m of DPD [26]. Inactivation of DPD by eniluracil would eliminate the Michaelis-Menten portion of the elimination leaving a linear component. Oral administration of drugs often makes two-compartment models difficult to fit, as the absorption phase may obscure a rapid distribution phase. However, the irreversible inactivation of DPD by eniluracil makes a one-compartment model a more physiologically appropriate structural model. Previously reported pharmacokinetic parameters of 5-FU administered orally with eniluracil have been determined by noncompartmental analysis [15, 16, 21]. The pharmacokinetic parameters determined by two-stage estimation and population modeling using one-compartment models and reported here are similar to previously reported values [21].

Pharmacokinetic analysis of most food effect studies determines primarily C_{max}, T_{max}, and $AUC_{0-\infty}$ by noncompartmental methods [27, 28, 29]. The merits of average, individual, or population bioequivalence for regulatory purposes have recently been discussed [30, 31]. Recently, Zhou et al. have used noncompartmental analysis to determine that food decreases the bioavailability of tegaserod by 50%, then utilized a NONMEM model to distinguish a decrease in the extent of absorption from the rate of absorption [32]. Jorga et al. have used a population approach to determine the effects of food on the pharmacokinetics of tolcapone in a parkinsonian population [33]. This allowed the effect of food to be determined in a small number of patients with a limited number of plasma samples.

In this study, analysis of the data using a population analysis approach allowed all the data to be fitted

simultaneously in order to differentiate between interindividual variability and intraindividual variability and with food as a covariable for each pharmacokinetic parameter independently. In contrast, analysis with noncompartmental or two-stage estimation determined means with a distribution and required the separate analysis of data from each subject for each treatment period. Errors in the fit from modeling any parameter from any individual subject will alter the mean pharmacokinetic parameters and affect the variability in the model.

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