W4402

Effect of Food on the Pharmacokinetics of Ulifloxacin, a Fluoroquinolone for Bacterial Gastroenteritis Treatment, in Healthy Subjects After Oral Dosing of the Prodrug Prulifloxacin

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ABSTRACT

Purpose:

To investigate the effect of food on the pharmacokinetics (PK) of ulifloxacin in healthy individuals following a single oral dosing of the prodrug prulifloxacin at 600 mg.

Methods:

Forty-two subjects were randomized to receive one 600 mg prulifloxacin tablet during either fasting or 30 minutes of a high-fat breakfast in 2 sequences with at least a 72-hour washout period. The plasma and the urine samples were collected over 48 hours and were analyzed for ulifloxacin using a validated HPLC-MS/MS assay. The PK parameters were determined by standard model independent methods. Analysis of variance was carried out using log transformed plasma C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$. The effect of food was assessed by examining the 90% confidence interval (CI) for the ratios of the test group means (fed) relative to the reference group means (fasted) for C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$. The K_{elim} was statistically evaluated by the paired t-test and T_{max} was evaluated by the Wilcoxon signed rank test with significance set at ≤ 0.05 for both tests.

The amount and percent excreted in urine and renal clearance were evaluated by the paired t-test.

Results:

Ulifloxacin median T_{max} values were 1.50 (range 0.5 to 3) hours and 2.52 (range 1 to 10.5). LSGM for ulifloxacin C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$ were 1200 and 1840 ng/mL, 9690 and 10400 ng•h/mL and 9830 and 10500 ng•h/mL for the fed and fasted state, respectively. The %Ratio of test-to-reference LSGM was 65.02% for the C_{max}, 93.21% for $AUC_{(0-T)}$ and 93.25% for $AUC_{(0-inf)}$. The corresponding 90% CI for those ratios were 57.75% to 73.20% for C_{max}, 85.00% to 102.22% for $AUC_{(0-T)}$ and 85.14% to 102.14% for $AUC_{(0-inf)}$. The AUC ratios are within the 80 to 125% CI limit of the fasted state. The C_{max} ratios are not within 80 to 125% CI limit of the fasted state. There were no statistical significant differences ($p \geq 0.05$) for K_{elim} or the urine parameters between fed and fasted state.

Conclusions:

Food ingestion delayed and reduced C_{max} of ulifloxacin, but did not affect AUC. Ulifloxacin K_{elim} and urine PK parameters did not change as result of food ingestion

Objective

To investigate the effect of food on the pharmacokinetics (PK) of ulifloxacin in healthy individuals following a single oral dosing of the prodrug prulifloxacin at 600 mg.

Introduction

Prulifloxacin, a new broad-spectrum fluoroquinolone antibacterial agent, is being developed by Optimer Pharmaceuticals to treat bacterial gastroenteritis. Prulifloxacin is orally absorbed and metabolized in the liver by an α-esterase (paraoxonase) to the active form, ulifloxacin (Tougou et, al., 1998; Keam and Perry. 2004; Prats et, al., 2006).

Ulifloxacin, displayed a potent in vitro activity against the most commonly gastroenteritis producing bacterial pathogens with an antibacterial activity 2-4x more potent than ciprofloxacin (Fritsche et, al., 2009).

Prulifloxacin has been approved for the treatment of gastroenteritis including infectious diarrheas in Japan at therapeutic dose of 600 mg once daily.

This poster presents the PK of ulifloxacin in a study that evaluated the effect of food on ulifloxacin PK following a single oral dosing of the prodrug prulifloxacin at 600 mg to healthy individuals.

Materials and Methods

A. Study

A Randomized, single-dose, two-period, crossover study that assesses safety and PK of ulifloxacin following a single oral dosing of the prodrug prulifloxacin at 600 mg to healthy volunteers during either fasted of fed states.

B. Dose

Forty-two subjects were randomized to receive one 600 mg prulifloxacin tablet during either fasting or 30 minutes of a high-fat breakfast in 2 sequences with at least a 72-hour washout period.

C. Analytical Method

The plasma and the urine samples were collected over 48 hours and were analyzed for ulifloxacin using validated HPLC-MS/MS assays.

D. PK Analysis

Plasma PK parameters (C_{max}, T_{max}, K_{elim}, $T_{1/2}$, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$) and urine PK parameters (the cumulative amount of ulifloxacin excreted in the urine over 48 hours ($Ae_{(0-48)}$), % ulifloxacin excreted in the urine in 48 hours relative to ulifloxacin-equivalent dose and the ulifloxacin renal clearance (CLR) were determined using WinNonlin Professional 5.2.1 (Pharsight Corp., Mountain View, CA).

Analysis of variance was carried out using log-transformed plasma C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$. The effect of food was assessed by examining the 90% confidence interval (CI) for the ratios of the test group means (fed) relative to the reference group means (fasted) for C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$.

The K_{elim} was statistically evaluated by the paired t-test and T_{max} was evaluated by the Wilcoxon signed rank test with significance set at ≤ 0.05 for both tests. The amount ($Ae_{(0-48)}$) and percent excreted in urine and CLR of ulifloxacin were evaluated by the paired t-test.

Results

PK of Ulifloxacin in Plasma:

Ulifloxacin median T_{max} values were 1.50 (range 0.5 to 3) hours for fasted and 2.52 (range 1 to 10.5) hours for fed state (Table 1). Corresponding harmonic $T_{1/2}$ mean values were 8.42 ± 1.22 hours and 8.20 ± 1.15 hours. Mean C_{max} values were 2000 ± 856 and 1260 ± 443 ng/mL, $AUC_{(0-T)}$ values were 10900 ± 3500 and 9920 ± 2140 ng•h/mL and $AUC_{(0-inf)}$ values were 11100 ± 3500 and 10100 ± 2130 ng•h/mL, respectively.

The C_{max}, $AUC_{(0-T)}$ and $AUC_{(0-inf)}$ Least Squares Geometric Means (LSGM) are presented in Table 2. The %Ratio of test-to-reference LSGM was 65.02% for the C_{max}, 93.21% for $AUC_{(0-T)}$ and 93.25% for $AUC_{(0-inf)}$. The corresponding 90% CI for those ratios were 57.75% to 73.20% for C_{max}, 85.00% to 102.22% for $AUC_{(0-T)}$ and 85.14% to 102.14% for $AUC_{(0-inf)}$. The AUC ratios are within the 80 to 125% CI limit of the fasted state. The C_{max} ratios are not within 80 to 125% CI limit of the fasted state. Ulifloxacin Tmax was statistically significant between the two treatments while the Kelim was not ($p \leq 0.05$) (Table 3).

PK of Ulifloxacin in Urine:

Ulifloxacin mean Ae(0-48) values were 127 ± 32.1 and 134 ± 42.4 mg which correspond to percent urinary excretion of 28.1 ± 7.09% and 29.6 ± 9.38% in the fed and fasted states, respectively (Table 4). Corresponding mean CLR values were 216 ± 40.3 and 208 ± 40.5 mL/min. The CLR values exceeded the glomerular filtration rate (GFR) of 100 mL/min and indicate that tubular secretion markedly contributes to the renal elimination of ulifloxacin.
There were no statistical significant differences for ulifloxacin Ae(0-48), %Excreted and CLR between the fed and fasted state ($p \geq 0.05$) (Table 5).

The 48 hour urine collection period accounted for the majority of the ulifloxacin renal elimination as evidenced from the fact that the cumulative excretion approached an apparent plateau by that time (Figure 3).

Figure 2

Mean Plasma Concentration-Time Profiles of Ulifloxacin in Human Subjects Following a Single 600 mg Oral Dose of Prulifloxacin in the Fasted and Fed States

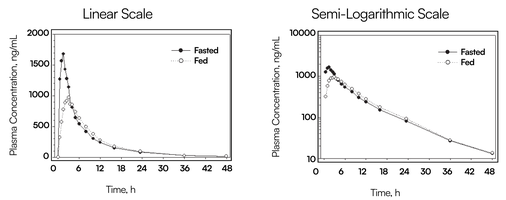

Figure 3

Mean Cumulative Urinary Excretion (mg or % Ulifloxacin-equivalent Dose) of Ulifloxacin in Human Subjects Following a Single 600 mg Oral Dose of Prulifloxacin in the Fasted and Fed States

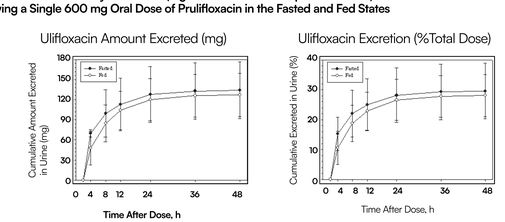

Figure 1

Chemical Structure of the Prodrug Prulifloxacin and its Active Metabolite, Ulifloxacin

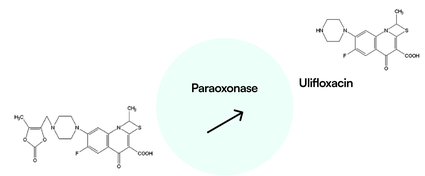

Table 1

* T1/2 is expressed as a harmonic mean and pseudo SD
Four subjects did not receive both treatments and were excluded from the assessments of the food effects

Summary of Ulifloxacin Plasma PK Parameters in Human Subjects Following a Single 600 mg Oral Dose of Prulifloxacin in the Fasted and Fed States

Treatment Group	Statistic	C_{max} (ng/mL)	T_{max} (h)	$AUC_{(0-T)}$ (ng•h/mL)	$AUC_{(0-inf)}$ (ng•h/mL)	K_{elim} (h-1)	$T_{1/2}$ (h-1)
Fasted	N	38	38	38	38	38	38
	Mean	2,000	1.45	10,900	11,100	0.0823	8.42*
	SD	856	0.676	3,500	3,500	0.0119	1.22*
	Min	712	0.500	5,320	5,430	0.0603	6.18
	Median	1,720	1.50	10,900	11,100	0.0797	8.70
	Max	3,960	3.00	20,000	20,100	0.112	11.5
	CV%	42.7	46.7	32.0	31.6	14.5	13.9
Fed	N	38	38	38	38	38	38
	Mean	1,260	2.98	9,920	10,100	0.0845	8.20*
	SD	443	1.80	2,140	2,130	0.0118	1.15*
	Min	706	1.00	5,450	5,660	0.0638	6.23
	Median	1,080	2.52	10,000	10,200	0.0827	8.39
	Max	2,920	10.5	15,400	15,400	0.111	10.9
	CV%	35.2	60.6	21.5	21.2	14.0	13.5

Table 3

* Geometric mean ratio of PK parameter in fed/fasted; expressed as a percent

Bioequivalence Evaluation of Ulifloxacin C_{max} and AUC in Human Subjects

Parameter	Treatment	Geometric Least Squares Means	GMR*	90% CI for GMR	
				Lower	Upper
C_{max}	Fasted	1,840	65.02	57.75	73.20
	Fed	1,200			
$AUC_{(0-T)}$	Fasted	10,400	93.21	85.00	102.22
	Fed	9,690			
$AUC_{(0-inf)}$	Fasted	10,500	93.25	85.14	102.14
	Fed	9,830			

Table 3

* Statistical significance set at ≤ 0.05 for both tests
[b] T_{max} value is expressed as median and range

Statistical Evaluation of Ulifloxacin T_{max} and K_{elim} in Human Subjects Following a Single 600 mg Oral Dose of Prulifloxacin in the Fasted and Fed States

Parameter	N	Treatment	Mean	SD	Statistical Test	p-value*
K_{elim}, h^{-1}	38	Fasted	0.0823	0.0119	Paired t-test	0.2391
	38	Fed	0.0845	0.0118		
T_{max}, h[b]	38	Fasted	1.50	0.5-3	Wilcoxon Signed Rank Test	0.0001
	38	Fed	2.52	1-10.5		

Table 4

* Geometric mean ratio of PK parameter in fed/fasted; expressed as a percent

Summary of Ulifloxacin Urine PK Parameters in Human Subjects Following a Single 600 mg Oral Dose of Prulifloxacin in the Fasted and Fed States

Parameter	Fasted			Fed		
	$Ae_{(0-48)}$ mg	%Total Excretion	CL_R mL/min	$AE_{(0-48)}$ mg	%Total Excretion	CL_R mL/min
N	38	38	38	38	38	38
Mean	134	29.6	208	127	28.1	216
SD	42.4	9.38	40.5	32.1	7.09	40.3
Min	61.7	13.6	101	64.1	14.2	107
Median	139	30.7	204	127	28.1	215
Max	212	46.8	311	216	47.7	301
CV%	31.6	31.6	19.5	25.2	25.2	18.7

Table 5

* Statistical significance set at ≤ 0.05

Statistical Evaluation of Ulifloxacin Urine PK Parameters in Human Subjects Following a Single 600 mg Oral Dose of Prulifloxacin in the Fasted and Fed States

Parameter	N	Treatment	Mean	SD	Statistical Test	p-value*
$Ae_{(0-48)}$ mg	38	Fasted	134	42.4	Paired t-test	0.4194
	38	Fed	127	32.1		
%Total Excretion	38	Fasted	29.6	9.38	Paired t-test	0.4198
	38	Fed	28.1	7.09		
CL_R mL/min	38	Fasted	208	40.5	Paired t-test	0.2664
	38	Fed	216	40.3		

Conclusions

Food ingestion delayed and reduced C_{max} of ulifloxacin, but did not affect AUC. Ulifloxacin K_{elim}, $Ae_{(0-48)}$, percent urinary excretion and CLR parameters did not change as result of food ingestion.

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