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 (600 mg).

Methods:

Fifty-two subjects were randomized to receive one 600 mg oral prulifloxacin tablet either fasting or 2 hours after a high-fat meal. 24 plasma samples were collected at 0.5, 1, 1, 2, 2, 3, 4, 6, 8, 10, 12, 12, 24, 24, 36, 48, 72, and 112 hours post-dosing for 151 subjects.

Results:

PK of Ulifloxacin in Plasma:

Ulifloxacin median \( t_{\text{max}} \) values were 1.02 (range 0.03 to 3.00) hours for the fasted and 2.08 (range 1.0 to 10.50) hours for the fed state. The \( t_{\text{max}} \) mean values were 0.57 ± 0.30 and 2.52 ± 1.15 hours. The corresponding R0% of those values were 97.0% (range 92.2% to 102.9%) and 93.25% (range 80.48% to 106.05%), respectively. The \( t_{\text{1/2}} \) mean values were 8.42 ± 1.22 hours and 8.20 ± 1.15 hours. Mean \( C_{\text{max}} \) values were 216 ± 40.3 and 208 ± 9.9 ng/mL, respectively. The \( C_{\text{max}} \) mean values were 1110 ± 350 and 1260 ± 443 ng/mL, respectively. The %Ratio of \( C_{\text{max}} \) between the fed and fasted state (p < 0.05).

PK of Ulifloxacin in Urine:

The ulifloxacin amount excreted in the urine over 48 hours (Ae) was statistically evaluated by the paired t-test and T-statistic was 19.12, mean values were 40.5 mL/min. The CL\( \text{RO} \) values did not change significantly between the fed and fasted state. The mean values were 216 ± 40.3 and 208 ± 9.9 ng/mL, respectively. The %Ratio of \( C_{\text{max}} \) between the fed and fasted state (p < 0.05).

Conclusions:

Food ingestion delayed and reduced \( C_{\text{max}} \) of ulifloxacin, but did not affect AUC. Ulifloxacin \( K_{\text{RO}} \) and AUC \( \text{RO} \) parameters did not change as much as \( C_{\text{max}} \).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 the 48th hour (Figure 3).

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Introduction

Prulifloxacin, a new broad-spectrum fluoroquinolone anti-infective agent, is being developed by Optimier Pharmaceuticals to treat bacterial gastroenteritis.

Prulifloxacin is orally absorbed and metabolized in the liver by an esterase (paraoxonase) to the active form, ulifloxacin (Tougou et al., 2011). Ulifloxacin has been approved for the treatment of gastroenteritis including infectious diarrheas in Japan at therapeutic dose of 600 mg once daily.

Materials and Methods

A. Study

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

B. Dose

Fifty-two subjects were randomized to receive one 600 mg prulifloxacin tablet either fasting or 2 hours after a high-fat meal. 24 plasma samples were collected at 0.5, 1, 1, 2, 2, 3, 4, 6, 8, 10, 12, 12, 24, 24, 36, 48, 72, and 112 hours post-dosing for 151 subjects.

C. Analytical Method

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

D. PK Analysis

Plasma PK parameters were estimated using non-compartmental analysis. A two-compartment model was used to describe the plasma concentration data. The areas under the curve were calculated using the trapezoidal rule. The %Ratio of PK parameters in fed/fasted; expressed as a percent geometric mean ratio of PK parameter in fed/fasted.

Conclusions:

Food ingestion delayed and reduced \( C_{\text{max}} \) of ulifloxacin, but did not affect AUC. Ulifloxacin \( K_{\text{RO}} \) and AUC \( \text{RO} \) parameters did not change as much as \( C_{\text{max}} \).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 the 48th hour (Figure 3).

References

