

Single and Multiple Ascending-dose Studies of Oral Delafloxacin: Effects of Food, Sex, and Age

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ABSTRACT

Purpose: The objective of this report is describe the results of 2 studies that examined the pharmacokinetic parameters, safety profile, and tolerability of single and multiple ascending doses of oral delafloxacin and the effects of food, sex, and age on oral delafloxacin pharmacokinetic parameters, safety profile, and tolerability.

Methods: The first study contained 3 parts and used unformulated delafloxacin in a capsule. Part 1 was a randomized, double-blind, placebo-controlled, single (50, 100, 200, 400, 800, 1200, and 1600 mg) ascending-dose study of oral delafloxacin in healthy men. Part 2 was a single-dose crossover study in which 20 men received 250 mg delafloxacin with or without food. Part 2 also included a parallel group, double-blind, placebo-controlled study in 16 women and 16 elderly men and women who were randomized (3:1) to receive 250 mg delafloxacin or placebo. Part 3 was a randomized, double-blind, placebo-controlled, multiple (100, 200, 400, 800, 1200 mg once daily for 5 days) ascending-dose study of oral delafloxacin in healthy men. The second study was a single-dose, randomized, 3-period crossover study in which participants received 900 mg delafloxacin (2 × 450-mg tablets) under fasted conditions, with a high-fat meal, or fasted with a high-fat meal 2 hours after dosing. Serial blood samples were collected, and plasma pharmacokinetic parameters of delafloxacin were determined.

Findings: Delafloxacin C_{max} and $AUC_{0-\infty}$ increased with increasing oral dose over the dose range of 50 to 1600 mg. The increases in delafloxacin $AUC_{0-\infty}$ were dose proportional at doses of ≥ 200 mg. Steady state was reached by day 3 of dosing with minimal accumulation of delafloxacin. The C_{max} of delafloxacin was decreased slightly in the presence of food. No sex difference in delafloxacin pharmacokinetic parameters

was observed. In the elderly men and women, mean delafloxacin C_{max} and $AUC_{0-\infty}$ were 35% higher than observed for young adults, which could be partially explained by a decrease in the creatinine clearance in the elderly men and women. Delafloxacin was well tolerated at the tested doses, with gastrointestinal adverse effects observed more commonly at doses ≥ 1200 mg.

Implications: Delafloxacin exhibits linear pharmacokinetic parameters that reached steady state after 3 days of daily oral dosing with minimal accumulation. Delafloxacin was well tolerated throughout both studies, with gastrointestinal effects observed at the higher doses (≥ 1200 mg). (*Clin Ther.* 2016;38:39–52) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: delafloxacin, food, elderly, pharmacokinetics, sex, tolerability.

INTRODUCTION

Delafloxacin (RX-3341, ABT-492, WQ-3034) is an investigational fluoroquinolone antibiotic with a broad spectrum of activity against gram-positive pathogens (methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant strains of *S aureus*, *Streptococcus pyogenes*, and *Streptococcus enterococci*), gram-negative pathogens (*Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa*), and anaerobes.^{1–3} The bactericidal action of delafloxacin results from dual inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA

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replication, transcription, repair, and recombination.^{4,5} Delafloxacin has an anionic structure, which may be a potential advantage over other fluoroquinolones in that its antibactericidal potency is increased under acidic conditions.^{6,7} This could be a benefit in the treatment of infections such as *S aureus*, which can survive in mildly acidic environments.⁷ In a randomized Phase II trial comparing 2 doses of intravenous delafloxacin with tigecycline in patients with various complicated skin and skin-structure infections, IV delafloxacin given at 300 mg or 450 mg every 12 hours produced clinical cure rates comparable to tigecycline.⁸ In a separate Phase II study, in patients with acute bacterial skin and skin structure infections (ABSSSIs), cure rates were similar between delafloxacin and linezolid but statistically greater with delafloxacin versus vancomycin.⁹ In these 2 Phase II studies, delafloxacin was well tolerated, with the most frequent adverse events (AEs) reported being nausea, vomiting, and diarrhea. Currently, delafloxacin is in Phase III trials being developed both as an intravenous and oral treatment of ABSSSIs.¹⁰

The present report describes the results of 2 studies conducted to evaluate the safety profile, tolerability, and pharmacokinetic parameters of oral doses of delafloxacin. The first study was a single and multiple ascending-dose study that included evaluations of the effects of food, sex, and age. In this first study, delafloxacin was administered as an unformulated chemical in a gelatin capsule. The second study was a food-effect study. The second study used delafloxacin in a formulated tablet, which is the same tablet formulation currently being used in a Phase III study on the treatment of ABSSSI with intravenous and oral delafloxacin.

PATIENTS AND METHODS

Both studies were conducted according to good clinical practice and followed the ethical principles of the Declaration of Helsinki. An independent ethics committee (Integreview, Austin, TX, and Guy's Research Ethics Committee, London, United Kingdom) approved the study protocols and all amendments. Written informed consent was signed by all the participants.

Study Participants

Study participants were healthy based on medical history, physical examination, clinical laboratory

evaluations, and 12-lead ECG. Participants were able to comply with the protocol and had a body mass index >18 through 28 kg/m² (18–30 kg/m² for the food-effect study). In the 3-part dose-escalation study, participants were men and women 18 through 40 years of age; elderly individuals were ≥65 years of age. In the food-effect study, men and women 18 through 55 years were included. Women were postmenopausal, surgically sterile, or used adequate contraception. Participants were nonsmokers and willing to abstain from alcohol, caffeine, grapefruit, or grapefruit juice (ascending-dose study) and methylxanthine-containing beverages or food (food-effect study).

The following individuals were excluded: those who had history of adverse reactions to quinolone antibiotics; those with evidence of clinically significant disease; those undergoing any surgical procedure that would interfere with gastric motility, pH, or absorption; those with gastric upset 1 week before the study start; those with a positive drug or alcohol screen result; users of prescription or over-the-counter medications; those with positive hepatitis A IgM, hepatitis B antigen, hepatitis C antibody, or HIV test results; or users of known inhibitors or inducers of drug metabolism 1 month before the start of the study. Individuals who used >2 g/d of acetaminophen were excluded from the food-effect study.

Single and Multiple Ascending-Dose Study (Unformulated Drug in Capsule)

This was a Phase 1, single-center study that consisted of 3 parts. Part 1 was a randomized, parallel-group, placebo-controlled study to evaluate the safety profile, tolerability, and pharmacokinetic parameters of single ascending oral doses of delafloxacin in healthy mean (aged 18–40 years). Fifty-six men were assigned 1 of 7 dose groups (50, 100, 200, 400, 800, 1200, and 1600 mg). In each dose group, 8 men were randomly assigned in a 3:1 ratio to receive a single oral dose of delafloxacin (n = 6) or placebo (n = 2). The dosing schedule was such that successively higher doses of delafloxacin were given after the safety profile of the preceding dose was determined. Delafloxacin was administered in the morning after an overnight fast of at least 8 hours.

Part 2 was designed to determine the effect of food on the bioavailability of delafloxacin and to assess the safety profile, tolerability, and pharmacokinetic parameters of delafloxacin in women and healthy elderly

people. The food-effect study was a randomized, single-dose, double-blind, 2-period crossover study. A total of 20 healthy men received delafloxacin (250 mg) or placebo in a 4:1 ratio and were fed (standardized high-fat breakfast 30 minutes before dosing) in one period and fasted (overnight for at least 8 hours) in the other period. A washout of 14 days separated the 2 periods. The study in healthy women (18–40 years of age) and elderly people (≥ 65 years of age) was a randomized, single-dose, parallel-group, double-blind, placebo-control study. Half of the elderly participants were female and half were male. A total of 16 women and 16 elderly women were randomized 3:1 to receive a single dose of delafloxacin (250 mg) or placebo under fasting conditions.

Part 3 of the study was a multiple ascending-dose trial of delafloxacin (100, 200, 400, 800, and 1200 mg) or placebo administered once daily for 5 days to fasting, healthy men (18–40 years of age). Sixty individuals were assigned to parallel groups of 12 people each. In each dose group, participants were randomly assigned 2:1 to delafloxacin or placebo. The dosing schedule was designed such that successively higher doses were administered after the safety of the preceding dose had been determined. Participants in parts 1 and 2 were confined to the study unit for the day before dosing through 48 hours after dosing. Participants in part 3 were confined to the study unit for 7 days, from the day before dosing to 48 hours after the last dose.

Food-Effect Study (Tablet Formulation)

This food-effect study was a Phase I, single-dose, randomized, open-label, 3-period, 6-sequence crossover study in 30 healthy men and women. Participants were randomly assigned to 1 of 6 treatment sequences in which a single 900-mg (2×450 -mg formulated tablet) oral dose of delafloxacin was given under the following 3 conditions: (1) after an overnight fast of at least 10 hours, (2) after an overnight 10-hour fast followed by a standardized high-fat breakfast 30 minutes before dosing, and (3) an overnight 10-hour fast followed by a high-fat meal 2 hours after dosing. The study consisted of a screening period, 3 treatment periods, and end-of-study or early termination period. There was at least a 7-day washout between each treatment period.

The standardized high-fat breakfast for both food-effect studies consisted of 2 eggs fried in butter, 2

strips of bacon, 2 slices of toast with butter, 4 oz of hash brown potatoes, and 8 oz of whole milk.

Blood and Urine Sample Collection

For parts 1 and 2 (single dose) of the 3-part ascending-dose study, blood samples (10 mL) were collected before dosing and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 30, 36, and 48 hours after dosing. For part 3 (multiple dose), blood samples were collected before dosing each day from days 1 through 5 of dosing. Blood samples were also collected at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, and 24 hours after dosing on days 1 and 5. Two additional blood samples were collected at 36 and 48 hours after the day 5 dose. Plasma was prepared from blood by centrifugation. For part 1 of the ascending-dose study, urine samples were collected before dosing up to 1 hour before dosing and from 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 hours after dosing. For part 3, urine samples were collected before dosing (up to 1 hour before dosing on day 1) and during the interval of 0 to 24 hours after the last dose on day 5.

For the food-effect study, blood samples (10 mL) were collected before dosing and at 0.15, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 20, 24, 36, and 48 hours after each treatment. Plasma and urine samples were analyzed for delafloxacin concentrations.

Bioanalytical Methods

Plasma and urine samples were kept frozen at -20°C or colder. Samples from the 3-part ascending-dose study were analyzed for delafloxacin concentration using an LC-MS/MS method with a concentration range of 8.0 to 5366.3 ng/mL. Plasma and urine samples were acidified, spiked with internal standard, and extracted by partitioning with hexane:ethyl acetate (1:3, v/v). The extract was subjected to HPLC analysis using a Waters XTerra RP18 column, with a mobile phase consisting of acetonitrile:aqueous 0.1% formic acid (2:3, v/v). Quantitation was accomplished by triple quadrupole mass spectrometry and monitoring the precursor-to-product ion pairs m/z 441 \rightarrow 379 for delafloxacin and m/z 421 \rightarrow 359 for the internal standard. The mean accuracy ranged from 93.8% to 111.8%, and the precision of the assay ranged from 7.6% to 15.7%.

Plasma samples from the food-effect study with the tablet formulation were analyzed using a LC-MS/MS

method with an assay range of 5.00 to 5000 ng/mL. Samples were extracted with hexane:ethyl acetate using supported liquid extraction and analyzed by LC-MS/MS. Quantitation was accomplished by triple quadrupole mass spectrometry and monitoring the precursor-to-product ion pairs m/z 441→379 for delafloxacin and m/z 446→381 for the internal standard. The mean accuracy was within 85% to 115% of the theoretical accuracy, and the precision of the assay did not exceed 15%.

Pharmacokinetic Analysis

Pharmacokinetic parameters were calculated by noncompartmental methods using WinNonlin Version 6.2.1 software (Pharsight Corp, Mountain View, CA). The T_{\max} and C_{\max} were the observed values. The k_e was determined from the slope of a least-squared linear regression of the log of the plasma concentrations from the terminal log-linear phase. The AUC-time curve from time zero to the time of the last measurable concentration or until 24 hours after dosing (AUC_{0-t} or AUC_{0-24}) was calculated by the linear trapezoidal method. The AUC was extrapolated to infinite time (AUC_{ext}) by dividing the last measurable plasma concentration (C_t) by k_e . The $AUC_{0-\infty}$ was calculated as follows: $AUC_{\infty} = AUC_{0-t} + AUC_{\text{ext}}$. The CL/F was calculated by dividing the administered dose by the $AUC_{0-\infty}$ (single dose) or AUC_{0-24} (after 5 days of dosing). The apparent volume of distribution in the terminal phase was calculated as $CL/F \div k_e$. The accumulation ratio was the ratio of day 5 AUC_{0-24} to the day 1 AUC_{0-24} . The fraction of dose recovered as unchanged delafloxacin in urine was calculated as the total amount of delafloxacin recovered in urine (A_u) for the 48-hour interval after single dose or the 24-hour interval on day 5 divided by the total administered dose. Renal clearance was A_u/AUC_{0-48} after single dose or $A_u/0-AUC_{24}$ after multiple dose. Creatinine clearance was calculated according to method of Cockcroft and Gault.¹¹

Statistical Analysis

For the single and multiple ascending-dose study, statistical analysis was performed for log C_{\max} , log C_{\min} (day 5 only), log AUC, and log k_e . For dose-proportionality assessments, C_{\max} , AUC, and C_{\min} were dose normalized before log transformation. An ANCOVA with weight as a covariate was used for

testing the hypothesis of invariance of each pharmacokinetic variable with dose. The primary test was performed on a linear contrast in the dose-level effects, with the contrast chosen so that the test had good power for a trend with dose assuming a linear relationship between dose and response.

The effect of food was analyzed using an ANOVA for log-transformed C_{\max} and AUC and for T_{\max} . The ANOVA model included effects for sequence, subject nested within sequence, period, and dosing condition (fasting or fed). Two 1-sided test procedures were performed via a 90% CI method. The 90% CI for relative bioavailability was computed by exponentiating the end points of the CI for the difference of logarithm means.¹² A point estimate of relative bioavailability was obtained.

To assess the sex and age effects, 2 analyses were performed on log C_{\max} , log AUC, T_{\max} , and k_e . In the first analysis, a 2-way ANOVA model was used on data from younger men and women under fasting conditions. The model included the effects for sex, period, and their interaction. In the second analysis, a 2-way ANOVA model was used with classification by sex and age (young or elderly) and with interaction included on the data for all doses administered under fasting conditions. All tests for the 3-part study were performed at the 0.05 level, using the GLM and MIXED procedures of SAS/STAT software, version 6.12.¹³

For the food-effect study with the tablet formulation, to assess the effect of food in the fed states (test) to the fasted state (reference), a linear mixed-effect model was performed on the natural log-transformed values of AUC_{0-t} , $AUC_{0-\infty}$, and C_{\max} with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. The geometric least-squares (LS) mean ratios of the 2 test treatments to the reference treatment for AUC_{0-t} , $AUC_{0-\infty}$, and C_{\max} were calculated by the antilog of the LS mean difference of the natural log-transformed values. A 90% CI for each ratio was constructed as the antilog of the 90% CI of the LS mean difference. No adjustment was made for multiplicity. In addition, the geometric LS means and corresponding 90% CIs were computed for AUC_{0-t} , $AUC_{0-\infty}$, and C_{\max} by taking the antilog of the LS means and corresponding 90% CIs from the linear mixed-effect model on the natural logarithm of the corresponding pharmacokinetic parameters.

Safety Analysis

The safety profile was monitored at screening, baseline, and throughout the study by physical examinations, vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature), 12-lead ECGs, laboratory evaluations (serum chemical analysis; hematologic testing, including coagulation parameters; urinalysis), and the assessment of AEs.

For the single ascending-dose study parts 1 and 2, AEs and vital signs were monitored daily for 3 days after dosing and laboratory evaluations were monitored daily for 4 days after dosing. For the multiple ascending-dose study, AEs, vital signs, and concomitant medications were monitored daily for days 1 through 7, and laboratory evaluations were performed on days 1, 3, 5, and 7. Assessments of AEs, vital signs, concomitant medications, and laboratory evaluations were also made during the outpatient visit, which occurred on days 9 through 12 of the study. The 12-lead ECG was performed at baseline and 2, 4, 8, 24, and 48 hours after dosing for the single ascending-dose study and on days 1, 5, and 7 and at the outpatient visit on days 9 through 12 for the multiple ascending-dose study.

For the food-effect study, vital signs and clinical laboratory evaluations occurred before dosing and at the end of the study. A 12-lead ECG was taken before dosing and at 2 and 48 hours after each dose. AEs were monitored throughout the study.

RESULTS

Demographic Characteristics and Disposition of Study Participants

For the 3-part ascending-dose study, the demographic characteristics of the study participants are summarized in [Table I](#). A total of 152 adults (136 men and 16 women) and 16 elderly individuals (8 men and 8 women) were enrolled. All participants completed parts 1 (single ascending dose) and 2 (effect of food, sex, and age) of the study; 3 participants in the 1200-mg dose group prematurely discontinued part 3 (multiple ascending dose) of the study because of an AE of diarrhea of moderate intensity. A total of 30 participants were enrolled in the second food-effect study with the formulated tablet. All participants completed the study.

Pharmacokinetic Parameters

Single and Multiple Ascending Dose

The mean plasma concentration–time profiles after a single dose are shown in [Figure 1](#). The mean (SD) pharmacokinetic parameters are listed in [Table II](#). Delafloxacin was rapidly absorbed with a mean T_{\max} of 1 to 2.5 hours across dose groups. The plasma concentration profiles decreased monoexponentially for doses ≤ 100 mg and biexponentially for doses ≥ 200 mg. The mean half-life at the lower doses (50 and 100 mg) was ≤ 2.5 hours compared with 5.9 to 7.7 hours at doses ≥ 200 mg. Secondary peak plasma concentrations were observed in several individuals (data not given). The delafloxacin C_{\max} from the 50-mg to 1600-mg doses increased from 0.949 to 16.6 $\mu\text{g/mL}$, and the corresponding $\text{AUC}_{0-\infty}$ values increased from 1.82 to 81.7 $\text{h} \cdot \mu\text{g/mL}$, respectively. There was a significant trend for the dose-normalized C_{\max} to decrease with increasing dose ($P = 0.0005$). The AUC values were proportional to dose at doses ≥ 200 mg. Delafloxacin was excreted unchanged in the urine with the fraction of the dose recovered in urine tending to decrease with increasing dose (35.6% at 50 mg to 12.8% at 1600 mg).

The mean plasma concentration–time profiles of delafloxacin after multiple dosing are shown in [Figure 2](#). The mean (SD) pharmacokinetic parameters are listed in [Table III](#). After repeated dosing for 5 days, the peak plasma delafloxacin concentrations occurred between 0.5 and 4.0 hours. As observed after a single dose, with multiple dosing the dose-normalized C_{\max} also tended to decrease with increasing doses ($P = 0.0017$). C_{\min} values increased from 0.105 to 1.79 $\mu\text{g/mL}$ in the dose range of 100 to 1200 mg/day, with no significant trend for dose-normalized C_{\min} to change with dose ($P = 0.7936$). There was a significant trend for dose-normalized AUC to decrease with increasing dose, but the magnitude was not compelling ($P = 0.0076$). The AUC values were statistically higher on day 5 compared with AUC values on day 1 ($P = 0.0056$), but the mean accumulation ratio was no more than 1.24, indicating the accumulation was minimal with once-daily dosing. Visual inspection of trough delafloxacin concentrations indicated that a steady state was achieved after approximately 3 days of dosing ([Figure 2](#)). Mean trough concentrations on days 3 and 4 were not statistically different from those on day 5 ($P \geq 0.1527$). The harmonic mean elimination half-life, which ranged from 4.2 to 8.5 hours, appeared to lengthen with increasing dose, but statistical analysis

Table I. Demographic characteristics of the study participants.

Demographic Characteristic	Single and Multiple Ascending-Dose (Effects of Food, Sex, and Age) Study					
	Single Dose (n = 56)	Multiple Dose (n = 60)	Elderly (n = 16)	Young Woman (n = 16)	Food Effect Unformulated Drug (n = 20)	Food-Effect Study Formulated Tablet (n = 30)
Age, mean (SD) [range], y	25.2 (5.53) [19-40]	25.7 (4.48) [19-39]	72.9 (5.6) [65-84]	24.4 (5.2) [18-39]	23.3 (5.2) [18-37]	33.7 (10.19) [22-55]
Weight, mean (SD) [range], kg	75.6 (9.45) [60-90]	76.7 (7.83) [61-99]	70.7 (11.5) [71-90]	65.3 (7.6) [55-76]	73.8 (9.7) [59-88]	69.0 (12.15) [51.0-93.4]
Sex, No. (%)						
Male	56 (100)	60 (100)	8 (50)	0	20 (100)	11 (36.7)
Female	0	0	8 (50)	16 (100)	0	19 (63.3)
Race, No. (%)						
White	52 (92.9)	56 (93.3)	16 (100)	16 (100)	18 (90)	24 (80.0)
Black	1 (1.79)	3 (5.0)	0	0	2 (10)	6 (20.0)
Asian	2 (3.57)	0 (0.0)	0	0	0	0
Other	1 (1.79)	1 (1.67)	0	0	0	0

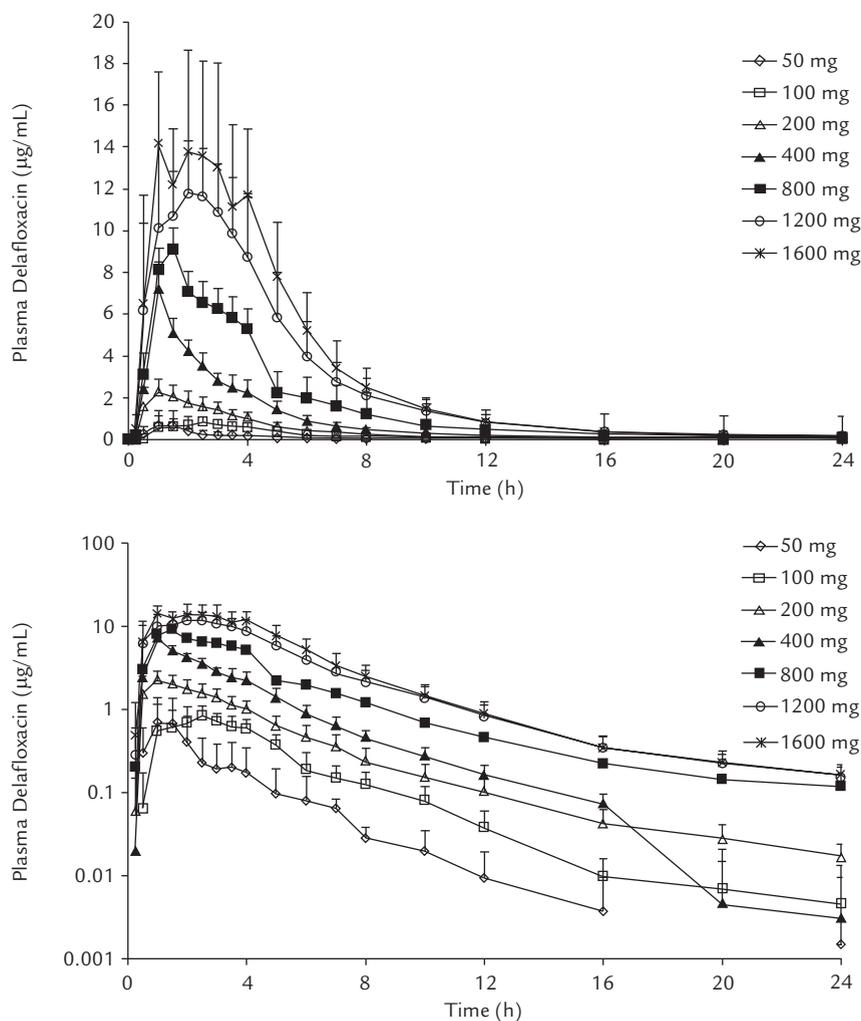


Figure 1. Mean plasma delafloxacin concentration-time profiles after a single oral dose of 50, 100, 200, 400, 800, 1200, and 1600 mg. Top, linear scale; bottom, semilogarithmic scale.

indicated no significant trend for k_e to change with dose ($P = 0.01812$). There was a time dependence in delafloxacin pharmacokinetic parameters because the mean half-lives tended to increase from day 1 to Day 5. Statistical analysis indicated that the elimination rate constants were lower on day 5 than on day 1 ($P = 0.0001$). Because the calculation of volume of distribution is dependent on k_e , V_z was larger on day 5 compared with day 1.

Effect of Age and Sex

The pharmacokinetic parameters for young and elderly men and women are given in Table IV. There

was no effect of age on T_{max} and k_e between young and elderly participants ($P \geq 0.0659$). The mean values for delafloxacin C_{max} and $AUC_{0-\infty}$ were statistically significantly higher in elderly participants compared with younger adults ($P \leq 0.001$). Because delafloxacin is cleared partially as unchanged drug in urine, an evaluation of C_{max} and $AUC_{0-\infty}$ values versus creatinine clearance was conducted. Plots of C_{max} and $AUC_{0-\infty}$ values versus creatinine clearance reveal a trend for these exposure parameters to increase with decreasing creatinine clearance (Figure 3). The coefficients of determination (R^2) for C_{max} and $AUC_{0-\infty}$ were 0.38 and 0.46, respectively.

Table II. Plasma pharmacokinetic parameters of delafloxacin after single ascending doses of oral delafloxacin (neat chemical in capsule) under fasting conditions.

Parameter	Delafloxacin, mg						
	50	100	200	400	800	1200	1600
T _{max} , median (range), h ^a	1.3 (1.0-1.75)	2.5 (1.0-3.0)	1 (0.5-3.0)	1.0 (1.0-1.0)	1.5 (1.0-3.5)	2.0 (1.0-3.0)	2.5 (1.0-3.0)
C _{max} , mean (SD), µg/mL	0.949 (0.181)	1.12 (0.303)	2.39 (0.620)	7.22 (1.26)	9.57 (2.14)	13.2 (2.50)	16.6 (3.83)
C _{max} per dose, µg/mL/mg	0.0189	0.0112	0.0120	0.0181	0.0120	0.011	0.010
AUC _{0-∞} , mean (SD), h · µg/mL	1.82 (0.342)	3.78 (0.954)	9.34 (2.01)	20.9 (2.96)	41.4 (10.8)	67.1 (17.2)	81.7 (18.5)
AUC _{0-∞} per dose, h · µg/mL/mg	0.036	0.038	0.047	0.052	0.052	0.056	0.051
t _{1/2} , h	1.5	2.5	5.9	6.2	7.7	5.5	7.2
CL/F, mean (SD), L/h	28.2 (5.1)	28.1 (8.3)	22.3 (4.8)	19.5 (3.0)	20.4 (5.0)	18.9 (4.8)	20.4 (4.4)
V _z /F, mean (SD), L	35.6 (7.0)	28.6 (4.9)	29.2 (6.8)	23.6 (3.7)	16.8 (2.5)	16.7 (2.4)	12.8 (4.1)
CL _r , mean (SD), L/h	10.1 (2.6)	8.0 (1.6)	6.6 (2.0)	4.7 (1.0)	20.4 (5.0)	18.9 (4.8)	20.4 (4.4)
f _e , mean (SD)	35.6 (7.0)	28.6 (4.9)	29.2 (6.8)	23.6 (3.7)	16.8 (2.5)	16.7 (2.4)	12.8 (4.1)

CL_r = renal clearance of delafloxacin; f_e = fraction of dose recovered as unchanged delafloxacin in urine; V_z/F = volume of distribution in the terminal phase.

The pharmacokinetic parameters of delafloxacin were comparable between men and women for both the young and elderly populations. Delafloxacin plasma concentrations were slightly higher in women than men, but the effects of sex and sex by elderly interaction were not significant for any of the pharmacokinetic parameters ($P \geq 0.5674$).

Effect of Food (Unformulated Drug in Capsule)

When delafloxacin (250 mg as unformulated chemical in a gelatin capsule) was administered with a high-fat meal compared with fasting conditions, the median T_{max} was delayed by 1.5 to 3 hours ($P = 0.0056$), the mean (SD) C_{max} was reduced by 50% from 3.58 (0.602) µg/mL to 1.86 (0.635) µg/mL, and the mean (SD) AUC was decreased by 15% from 13.6 (2.85) h · µg/mL to 11.4 (1.96) h · µg/mL.

Effect of Food (Formulated Tablet)

The pharmacokinetic parameters for delafloxacin (900 mg as 2 × 450-mg formulated tablets) given under fasting or fed conditions are given in Table V. Statistical analysis is presented in Table VI. When delafloxacin was given with a high-fat meal, C_{max} was reduced by 20.5% compared with fasting conditions. Total exposure (AUC_{0-t} and AUC_{0-∞}) was not affected by administration under fed conditions.

Safety Profile

The incidence of treatment-emergent AEs (TEAEs) was highest in the 1200-mg (5 of 6 participants [83%]) and 1600-mg (3 of 6 participants [50%]) groups for the single ascending dose and in the 800-mg (4 of 8 participants [50%]) and 1200-mg (7 of 8 participant [88%]) groups for the multiple ascending-dose portion of the study. Diarrhea was the most common TEAE reported, occurring in 3 of 6 participants at 1200 mg and 2 of 6 participants at 1600 mg in part 1 (single dose); 3 of 16 men, 2 of 12 women, and 2 of 12 elderly participants given 250 mg in part 2; and 1 of 8 participants at 100 mg, 5 of 8 participants at 200 mg, 1 of 8 participants at 400 mg, 4 of 8 participants at 800 mg, and 4 of 8 participants at 1200 mg in part 3 (multiple dose). The 3 participants at the 1200-mg once-daily dose had diarrhea of moderate intensity. All other incidents of diarrhea were of mild intensity. Rash was observed sporadically in the single (1 of 6 participants at 100 mg) and multiple (1 of 8 participants at 100 mg, 2 of 8 participants at 200 mg, and 3 of 8 participants at 1200 mg) ascending-dose

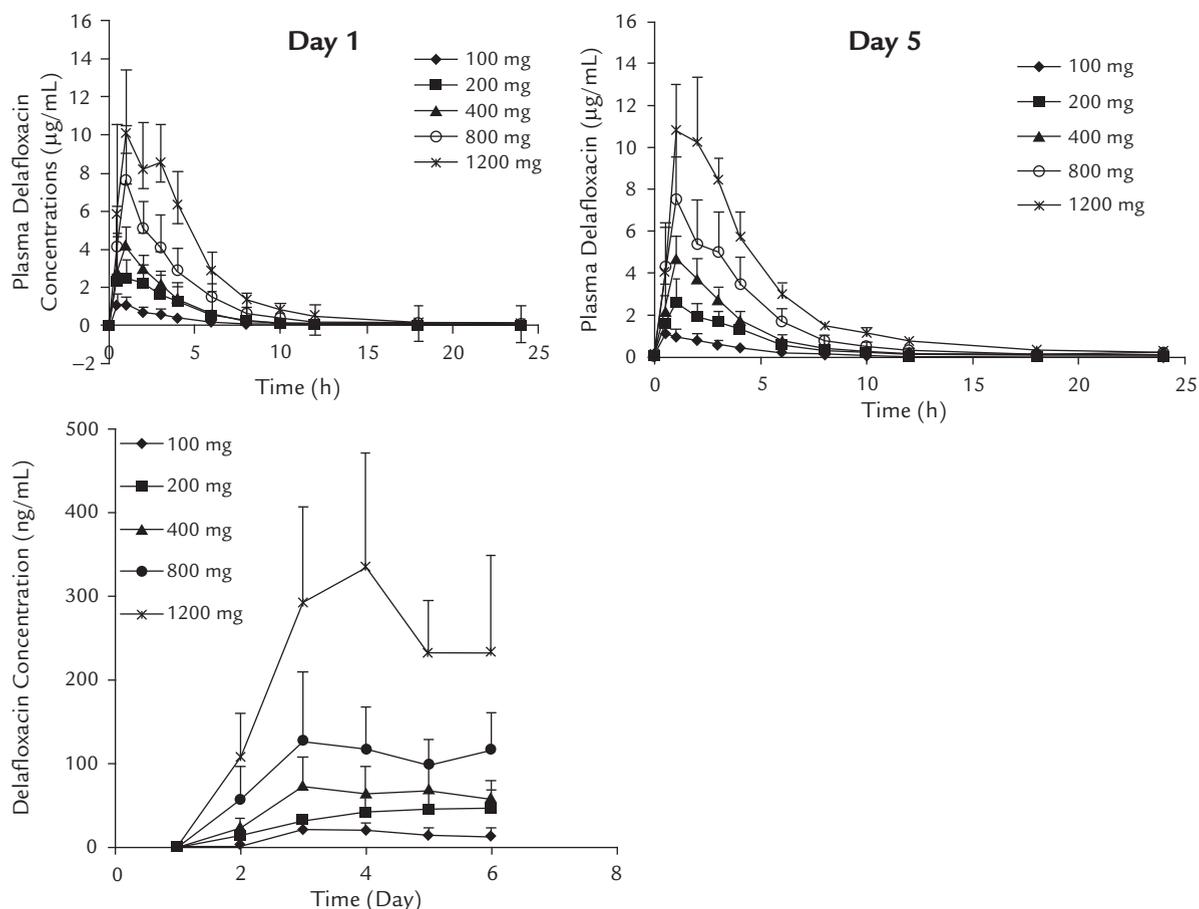


Figure 2. Mean plasma delafloxacin concentration-time profiles on day 1 (upper left) and day 5 (upper right). Mean plasma delafloxacin trough concentrations on days 1 through 6 (lower left) after administration of delafloxacin once a day at doses of 100, 200, 400, 800, and 1200 mg.

portions of the study but without a clear dose-response relationship. No important differences in the frequency or character of TEAEs were observed based on age, sex, or feeding status relative to the ascending dose portions of the study. Changes in laboratory findings and vital signs were minor and not considered clinically significant. In the multiple ascending-dose portion of the study, 7 of 40 delafloxacin-treated participants had values above the normal range for alanine aminotransferase (ALT), including 1 participant with an abnormal ALT value at baseline. Elevated values of ALT were observed after day 5, the end of dosing and confinement, and on days 7 (4 participants) and 9 (2 participants). One participant had elevated ALT values first observed on the last day of dosing. Two participants had elevated ALT values >2 times the upper limit of normal, but no participant had

elevations >3 times the upper limit of normal. No clear dose response was observed for participants with elevated ALT values, and most elevated ALT values tended to occur on day 9, which was 4 days after the end of dosing and confinement; therefore, the association of these elevations to study drug cannot be clearly established. No concomitant elevations of alkaline phosphatase were observed. Both the Bazett and Fridericia correction methods were used for QTc evaluation. No evidence of significant QTc interval prolongation with delafloxacin treatment was observed. Overall, delafloxacin was well tolerated at the single and multiple doses administered. Food, sex, and age did not appear to significantly affect the safety profile.

In the food-effect study with tablet formulation, TEAEs were reported by 7 participants (25.9%)

Table III. Pharmacokinetic parameters after multiple daily doses of oral delafloxacin (neat chemical in gelatin capsule).

Pharmacokinetic Parameter	Delafloxacin Once Daily, mg				
	100 (n = 8)	200 (n = 8)	400 (n = 8)	800 (n = 8)	1200 (n = 5)
Day 1					
T _{max} , median (range), h	1.0 (0.5–3.0)	0.8 (0.5–2.0)	1.0 (0.5–2.0)	1.0 (0.5–2.0)	1.0 (0.5–3.0)
C _{max} , mean (SD), µg/mL	1.36 (0.452)	3.17 (0.699)	4.49 (0.965)	8.18 (2.36)	11.5 (2.96)
C _{max} per dose, µg/mL/mg	0.0136	0.0159	0.0112	0.0102	0.0096
AUC _{0–∞} , mean (SD), (h · µg/mL)	4.06 (0.576)	11.2 (1.26)	14.8 (2.13)	28.0 (8.13)	50.6 (8.92)
AUC _{0–∞} per dose, (h · µg/mL/mg)	0.041	0.056	0.037	0.035	0.042
t _{1/2} , harmonic mean, h	3.2	3.8	4.1	4.3	4.5
CL/F, mean (SD), L/h	25.1 (3.7)	18.0 (2.0)	27.5 (4.0)	30.5 (7.9)	24.4 (4.4)
V _z /F, mean (SD), L	121.1 (32.2)	110.2 (39.8)	210.4 (139.6)	211.1 (89.1)	171.8 (77.4)
Day 5					
T _{max} , median (range), h	0.8 (0.5–2.0)	1.0 (0.5–4.0)	1.0 (1.0–2.0)	1.0 (0.5–2.0)	1.0 (1.0–2.0)
C _{max} , mean (SD), µg/mL	1.33 (0.460)	3.07 (0.810)	4.95 (0.947)	8.17 (2.16)	11.5 (2.02)
C _{max} per dose, µg/mL/mg	0.0133	0.0154	0.0123	0.0102	0.0096
C _{min} (µg/mL)	0.0105 (0.0105)	0.0395 (0.0141)	0.0523 (0.0188)	0.0963 (0.0301)	0.179 (0.0634)
AUC _{0–t} , mean (SD), h · µg/mL	4.46 (0.882)	11.5 (1.85)	17.8 (3.40)	31.4 (8.58)	54.3 (0.804)
AUC _{0–t} per dose, h · µg/mL/mg	0.0446	0.0575	0.0445	0.0393	0.0453
t _{1/2} , harmonic mean, h	4.2	7.4	8.4	8.5	7.6
CL/F, mean (SD), L/h	23.1 (4.1)	17.7 (2.6)	23.3 (4.8)	27.1 (7.2)	22.5 (3.6)
V _z /F, mean (SD), L	154.1 (60.6)	235.9 (142.2)	347.0 (222.5)	386.6 (197.5)	315.1 (186.4)
AR,* mean (SD)	1.10 (0.07)	1.03 (0.12)	1.24 (0.33)	1.15 (0.13)	1.18 (0.10)
f _e , mean (SD)	29.3 (13.5)	29.4 (11.3)	23.9 (14.4)	18.9 (25.9)	23.9 (9.3)
CL _r , mean (SD), L/h	5.9 (3.2)	5.9 (2.3)	6.2 (4.0)	7.1 (8.1)	4.2 (2.0)

AR = accumulation ratio; CL_r = renal clearance of delafloxacin; f_e = fraction of dose recovered as unchanged delafloxacin in urine; V_z/F = volume of distribution in the terminal phase.

*Day 5 AUC_{0–24}/day 1 AUC_{0–24}.

given delafloxacin (900 mg) under fasted conditions with a meal 2 hours after dosing, 6 participants (20.7%) after delafloxacin (900 mg) under fed conditions, and 4 (14.3%) after delafloxacin (900 mg) under fasted conditions. The most frequently reported TEAE was diarrhea (5 participants [16.7%]).

DISCUSSION

Delafloxacin is an investigational fluoroquinolone that is currently in Phase III development as an intravenous and oral product for the treatment of ABSSSIs. In 2

Phase II studies, delafloxacin given as an intravenous infusion provided comparable outcomes to approved comparators in the treatment of complicated skin and skin structures infections and ABSSSIs.^{8,9} In these 2 studies, delafloxacin was well tolerated, with the most common AEs reported being nausea, vomiting, and diarrhea. The oral formulation of delafloxacin allows for convenience and flexibility for the treatment of patients with skin infections.

The present report describes the first-in-human single and multiple ascending-dose trial of oral delafloxacin conducted in healthy volunteers. In this study, delafloxacin was administered as unformulated

Table IV. Effect of sex and age on the pharmacokinetic parameters of delafloxacin after a single oral 250-mg dose (neat chemical in capsule).

Pharmacokinetic Parameter	Young Men (n = 16)	Young Women (n = 12)	Elderly Men (n = 6)	Elderly Women (n = 6)
T_{max} , median (range), h [§]	1.0 (0.5–4.0)	1.0 (1.0–4.0)	1.0 (1.0–2.0)	1.0 (1.0–1.5)
C_{max} , mean (SD), $\mu\text{g/mL}$	3.58 (0.602)*	3.89 (1.27)*	4.62 (0.793)	5.30 (1.06)
$AUC_{0-\infty}$, mean (SD), $\text{h} \cdot \mu\text{g/mL}$	13.6 (2.85)*	14.4 (2.63)*	19.3 (4.84)	19.0 (3.55)
$t_{1/2}$, harmonic mean, h [†]	8.3	9.0	5.9	7.1
CL/F, mean (SD), L/h [‡]	19.3 (4.8)	17.8 (2.6)	13.7 (3.4)	13.6 (2.5)
V_z/F , mean (SD), L [‡]	444 (605)	551 (731)	158 (147)	164.6 (84.7)

V_z/F = volume of distribution in the terminal phase.

*Statistically significantly different from elderly individuals (ANOVA, $P < 0.05$).

[†]Evaluations of $t_{1/2}$ were based on statistical tests for k_e .

[‡]Parameter was not tested statistically.

[§]Median (minimum, maximum).

drug in a gelatin capsule under fasting conditions. The doses given covered a wide dose range after both single and repeated administration. Delafloxacin was

well tolerated, with the most common TEAE reported being gastrointestinal events (nausea, vomiting, and diarrhea). Delafloxacin at doses of ≥ 800 mg had the highest incidences of diarrhea. Some participants had ALT values above the normal range, but an association with study drug could not be established because there was no clear dose response and most of the elevations occurred 4 days after the end of dosing and confinement. Studies with larger numbers of patients and of longer duration are needed to fully assess the potential effects of delafloxacin on ALT. In Phase II studies of delafloxacin in patients with complicated skin and skin-structure infections and ABSSSIs, no clinically relevant treatment-related ALT elevations were observed.^{8,9} No evidence of QTc prolongation was observed, which is consistent with results from a thorough QTc study.¹⁴ Age, sex, or the administration of drug with food did not change the safety profile of delafloxacin.

Delafloxacin was rapidly absorbed after oral administration with peak concentrations occurring approximately 1 hour after dosing. At doses ≥ 200 mg, delafloxacin concentrations decreased in plasma in a biexponential manner with a terminal half-life of approximately 6 to 8 hours. At doses < 200 mg of plasma, delafloxacin decreased in a monoexponential manner with a short half-life (approximately 2 hours) likely due to the sensitivity limits of the assay preventing detection of the terminal elimination phase.

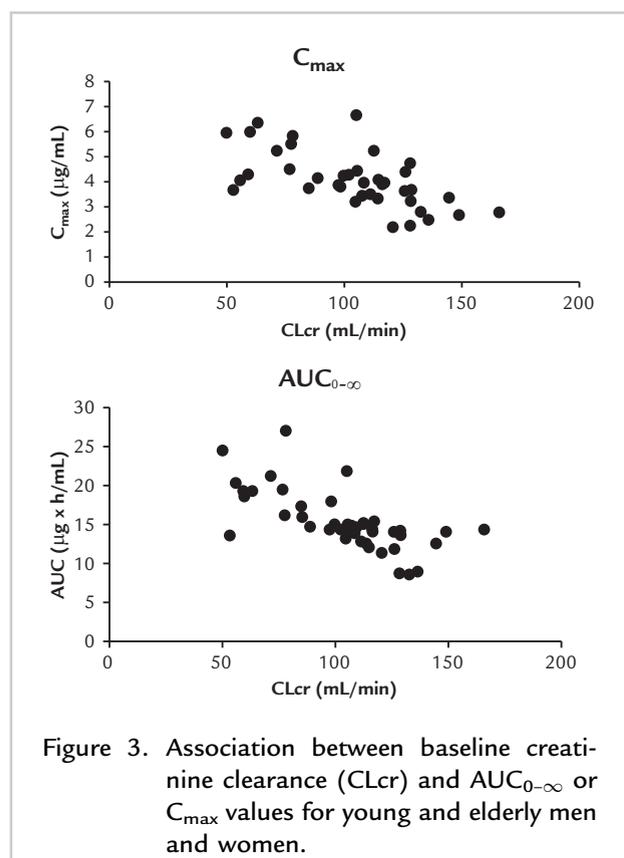


Figure 3. Association between baseline creatinine clearance (CLCr) and $AUC_{0-\infty}$ or C_{max} values for young and elderly men and women.

Table V. Pharmacokinetic parameters of delafloxacin after a single oral 900-mg dose (2 × 450-mg tablet): effect of food.

Parameter	Delafloxacin (900 mg, 2 × 450-mg Tablet)		
	Fasted (n = 28)	Fed (n = 20)	Fasted, With Meal 2 Hours After Dosing (n = 25)
T _{max} , median (range)	1.25 (0.50–4.00)	2.50 (1.00–6.00)	1.50 (0.50–2.50)*
C _{max} , mean (SD), µg/mL	11.5 (2.76)	9.14 (2.81)	11.8 (2.64)*
AUC _{0–t} , mean (SD), h · µg/mL	56.2 (15.21)	57.1 (14.15)	49.8 (12.01)
AUC _{0–∞} , mean (SD), h · µg/mL	55.2 (13.68)	58.2 (11.41)	52.2 (12.55) [†]

*n = 23.

[†]n = 9, 16, and 14 for fasted, fed, and fasted with a meal 2 hours after dosing, respectively.

The half-life of delafloxacin was longer after multiple doses compared with single-dose administration. This observation may be a result of data up to 48 hours being available for the day 5 estimation, whereas data only up to 24 hours were available for the day 1 estimation. Secondary peak plasma concentrations were observed in several participants, which may be due to enterohepatic cycling, also making it difficult to provide an accurate estimate of elimination half-life.

In a human intravenous radiolabeled delafloxacin mass balance study, approximately 28% of the administered radioactivity was excreted as unchanged delafloxacin in feces, which likely arose from biliary excretion and/or transintestinal elimination, suggesting the possibility of enterohepatic cycling.¹⁵ On multiple daily dosing, a steady state in delafloxacin plasma concentrations was reached in approximately 3 days with minimal accumulation (25%). The C_{max}

Table VI. Effect of food on the pharmacokinetic parameters of oral delafloxacin (tablet formulation).

Parameter	Treatment*	N	Geometric LS Estimate (90% CI)	Treatment Comparison	Geometric LS Mean Ratio, % (90% CI)
C _{max} , mean (SD), µg/mL	A	28	10.3 (9.41–11.3)		
	B	29	8.20 (7.50–8.96)	B/A	79.5 (73.1–86.4)
	C	23	10.5 (9.56–11.6)	C/A	102 (93.6–112)
AUC _{0–t} , mean (SD), h · µg/mL	A	28	51.4 (47.1–56.2)		
	B	29	52.3 (48.0–57.1)	B/A	102 (95.7–108)
	C	25	45.9 (41.9–50.3)	C/A	89.3 (83.8–95.1)
AUC _{0–∞} , mean (SD), h · µg/mL	A	9	49.5 (43.7–56.0)		
	B	16	52.0 (47.1–57.3)	B/A	105 (92.1–120)
	C	14	49.6 (44.6–55.2)	C/A	100 (86.7–116)

LS = least squares.

*Treatment A was 900 mg oral delafloxacin (2 × 450-mg formulated tablets), fasted; treatment B was 900 mg oral delafloxacin (2 × 450-mg formulated tablets), fed; and treatment C was 900 mg oral delafloxacin (2 × 450-mg formulated tablets), fasted, with a meal 2 hours after dosing.

of delafloxacin generally increased with increasing dose, and the AUC increased proportionally with dose at doses ≥ 200 mg.

There were no observed sex differences in delafloxacin pharmacokinetic parameters in the young and elderly populations. Systemic exposure to delafloxacin was higher in elderly individuals compared with young adults, which could be attributed in part to lower creatinine clearance in the elderly individuals. The correlation of delafloxacin exposure to creatinine clearance is expected because unchanged delafloxacin is partially eliminated by renal filtration. After intravenous administration of radio-labeled delafloxacin, approximately 66% of the dose is excreted in urine, most of which is unchanged delafloxacin.¹⁵ Delafloxacin clearance is also reduced in patients with moderate and severe renal impairment.¹⁶

The administration of ciprofloxacin with food results in delayed absorption.¹⁷ The absorption of fluoroquinolones, ciprofloxacin, and norfloxacin decreases when coadministered with milk or milk products.^{18,19} The effect of coadministration with a high-fat meal, including milk, on the pharmacokinetic parameters of delafloxacin was examined after administration of delafloxacin as an unformulated chemical in a gelatin capsule (250 mg) and in the tablet formulation (900 mg given as 2 \times 450-mg tablets). Delafloxacin T_{\max} was prolonged when given with food regardless of formulation, most likely due to a delay in stomach emptying. When given as unformulated chemical, C_{\max} was reduced significantly (50%), but total exposure was minimally decreased. When delafloxacin was administered in a formulated tablet with food, C_{\max} was reduced slightly (20%), but again total exposure (AUC) was not significantly changed. Consumption of a meal 2 hours after the administration of delafloxacin did not have a significant effect on its absorption. The food effect on C_{\max} is not considered clinically relevant because efficacy for delafloxacin, as with other fluoroquinolones, is likely more dependent on total and not peak exposure.^{20,21} These results indicate that delafloxacin can be given without regard to food when administered in the current formulated tablet.

CONCLUSIONS

In summary, delafloxacin was generally well tolerated when given orally to healthy volunteers over a wide dose range, with gastrointestinal AEs more commonly

observed with single doses of >1200 mg and with multiple doses of ≥ 800 mg. Delafloxacin was well absorbed with pharmacokinetic characteristics that are supportive of twice-daily dosing that is currently being evaluated in Phase III studies of ABSSSIs.

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AUTHOR CONTRIBUTIONS

Randy Hoover, Sue Cammarata, Eugene Sun contributed to the design, interpretation of data, and review of the manuscript. Laura Lawrence, Thomas Hunt, and Michael Benedict contributed to the food-effect study design, execution, and review of the manuscript. Susan K. Paulson contributed to the food-effect study design, wrote, and was compensated for writing the manuscript.

CONFLICTS OF INTEREST

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