Safety, Tolerability, and Pharmacokinetic Properties of Intravenous Delafloxacin After Single and Multiple Doses in Healthy Volunteers

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ABSTRACT

Purpose: The objective of this report was to determine the pharmacokinetic properties, safety, and tolerability of single and multiple doses of intravenous delafloxacin. In addition, the absolute bioavailability (BA) of the 450-mg tablet formulation of delafloxacin was determined.

Methods: Three clinical trials are summarized. The first study was a randomized, double-blind, placebo-controlled, single- (300, 450, 600, 750, 900, and 1200 mg) ascending-dose study of IV delafloxacin in 62 (52 active, 10 placebo) healthy volunteers. The second study was a randomized, double-blind, placebo-controlled study of IV delafloxacin (300 mg) given as a single dose on day 1, followed by twice-daily dosing on days 2 through 14; 12 (8 active, 4 placebo) healthy volunteers were enrolled. The third study was an open-label, randomized, 2-period, 2-sequence crossover study in which 56 healthy volunteers were randomly assigned to 1 of 2 sequences of a single oral dose of delafloxacin (450-mg tablet) or IV delafloxacin (300 mg). Serial blood samples were collected, and plasma pharmacokinetic parameters of delafloxacin were calculated.

Findings: Delafloxacin C_{max} values increased proportionally with increasing single IV dose for the dose range of 300 to 1200 mg, whereas the AUC values increased more than proportionally to dose for the same dose range. The mean terminal half-life of delafloxacin was approximately 12 hours (ranging from 8 to 17 hours). The volume of distribution (V_d) at steady state was approximately 35 L, which is similar to the volume of total body water. There was minimal accumulation of delafloxacin after twice-daily IV administration of 300 mg with an accumulation ratio of 1.09. The delafloxacin total exposure after a single 1-hour IV infusion of 300 mg and a single oral dose of a 450-mg tablet were equivalent with geometric least square mean ratio (90% CI) of 0.8768 (0.8356–0.9200) for $AUC_{0-\infty}$ and 0.8445 (0.8090–0.8815) for AUC_{0-t}, respectively. The C_{max} values of delafloxacin were not equivalent for the 2 formulations with a ratio (90% CI) of 0.5516 (0.5150–0.5908), respectively. The mean absolute bioavailability of delafloxacin was 58.8%.

Implications: Delafloxacin was well tolerated in healthy volunteers after single and multiple IV doses. The total systemic exposure to IV (300 mg) and oral (450 mg) delafloxacin is comparable, supporting that a switch between the 2 formulations is appropriate. (*Clin Ther*. 2016;38:53–65) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: bioavailability, delafloxacin, intravenous, pharmacokinetic properties, safety, tolerability.

INTRODUCTION

Delafloxacin (RX-3341, ABT-492, WQ-3034) is an investigational anionic fluoroquinolone antibiotic that is currently in Phase III development for the treatment of acute bacterial skin and skin structure infections (ABSSSIs). Delafloxacin has a broad spectrum of activity against gram-positive pathogens, including methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant strains of *S aureus* (MRSA), *Streptococcus pyogenes*, and enterococci, while maintaining activity against gram-negative pathogens and

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anaerobes.[1–3] Delafloxacin is unique in that its antibacterial potency increases as the pH of the local environment becomes more acidic, a characteristic of infection settings.[4]

Delafloxacin has excellent in vitro activity against MRSA, with an MIC_{90} ranging from 0.12 to 0.5 μg/mL.[5] In a Phase II study of ABSSSIs, intravenous delafloxacin had comparable cure rates with linezolid but statistically greater cure rates when compared with vancomycin.[6] In a second Phase II study of complicated skin and skin-structure infections, delafloxacin had comparable cure rates with tigecycline.[7] Delafloxacin has been generally well tolerated, with mild to moderate gastrointestinal adverse events (AEs) being most common.[6,7] Delafloxacin has a very low potential for phototoxicity and has no effect on the QT interval.[8,9] Both intravenous and oral formulations of delafloxacin are being developed, which would enable the possibility of patients to switch from intravenous to oral therapy. The doses of delafloxacin being evaluated in Phase III for treatment of ABSSSIs are 300 mg and 450 mg for IV and oral administration, respectively.

The disposition of delafloxacin after a single 300-mg IV dose has been studied in a mass-balance study using radiolabeled delafloxacin in healthy male volunteers.[10] Delafloxacin was predominantly excreted by the kidney, with 66% of a single intravenous dose recovered in the urine, most of which was unchanged delafloxacin. Approximately 29% of the radioactivity was recovered in the feces, which was likely due to biliary excretion and/or transintestinal elimination. Delafloxacin undergoes minimal oxidative metabolism, and excretion of acyl glucuronides in urine represented $\leq$20% of the administered intravenous dose.

The present report describes the results of 3 studies conducted to determine the safety, tolerability, and pharmacokinetic properties of intravenous delafloxacin after single and multiple doses in healthy volunteers. In addition, a comparative bioavailability study was conducted to determine whether systemic exposure to delafloxacin is equivalent for the IV 300-mg and oral 450-mg doses, which would support the appropriateness of a switch between the 2 formulations.

PATIENTS AND METHODS

The 3 studies reported here were conducted according to good clinical practice and all applicable guidelines following the ethical principles of the Declaration of Helsinki. An independent ethics committee reviewed and approved the protocol and written informed consent for each of the 3 studies. The volunteers signed written informed consent forms.

Study Population

Study participants were healthy male and female adults (18 to 64 years old) with a body mass index between 19 and 32 kg/m^2. Participants were enrolled based on review of medical history, physical examination, vital signs, clinical laboratory tests, and ECG. Participants were nonsmokers and did not have a history of drug or alcohol abuse. Female participants were not pregnant or breastfeeding. Concomitant medications were not allowed 14 days (or 7 days for over-the-counter medications) before study start and through completion of exit procedures. The use of intravenous or oral antibiotics within 4 weeks of first dose of study drug was prohibited.

Study Designs

The first study was a double-blind, randomized, single-ascending-dose study conducted in 62 healthy male and female volunteers. Twelve volunteers received a single IV 1-hour infusion of 300 mg of delafloxacin. The remaining 50 volunteers received a single IV 1-hour infusion of 450, 600, 750, 900, or 1200 mg delafloxacin (8 per dose group) or placebo (2 per dose group). Blood samples were collected before dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, 24, 36, and 48 hours after dosing. Urine samples for measurement of delafloxacin concentrations were collected before dosing and at 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 36, and 36 to 48 hours after dosing. The safety profile and tolerability of the preceding dose was confirmed before escalation to the next dose level.

The second study was a randomized, double-blind, placebo-controlled study to evaluate the pharmacokinetic properties, safety profile, and tolerability of multiple IV doses (300 mg infused for 1 hour) of delafloxacin in 12 healthy male and female volunteers. The volunteers received a single 300-mg IV infusion of delafloxacin (n = 8) or placebo (n = 4) on day 1. On days 2 through 14, delafloxacin (300 mg) was administered twice daily as two 1-hour infusions given 12 hours apart. Blood samples were collected on day 1 and day 14 before dosing, at 0.5 hours during the infusion, and at 1, 1.083, 1.167, 1.33, 1.5, 2, 3, 4, 5, 6, 8, 12, 16 (day 1 only), and 24 (day 1 only) hours after dosing. On days

3, 7, and 10, blood samples were collected just before the morning and evening doses. Urine samples were collected on day 1 (before dosing, at 0-12 hours after dosing, and at 12-24 hours after dosing) and on day 14 (before dosing, at 0-12 hours after dosing).

In the third study, the safety profile and tolerability of intravenous and oral delafloxacin were evaluated in an open-label, randomized, 2-period, 2-sequence crossover study. A total of 56 healthy male and female volunteers were randomly assigned in a 1:1 ratio to a single dose of oral delafloxacin (450-mg tablet) and IV delafloxacin (300 mg infused for 1 hour). Volunteers fasted at least 8 hours before delafloxacin administration and continued to fast until 4 hours after study drug administration. Blood samples were collected to determine delafloxacin plasma concentrations before dosing and at 0.25, 0.5, 0.75, 1 (end of infusion for intravenous, 1 hour after dosing for oral), 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, 24, 30, 36, 48, and 72 hours after dosing in each period.

The safety profile was monitored throughout the studies by physical examinations, vital signs, ECGs, laboratory evaluations, and the assessment of AEs. A sulfobutyl-ether-β-cyclodextrin (SBEβCD)*-containing formulation of intravenous delafloxacin was used in all 3 studies.

Bioanalytical Methods

Plasma and urine samples were extracted with hexane:ethyl acetate, analyzed using validated liquid chromatography–tandem mass spectrometry methods (assay ranges of 5.00 to 5000 ng/mL and 50.0 to 10000 ng/mL, respectively), and subjected to isocratic reverse-phase HPLC. Quantitation was accomplished by triple-quadrupole mass spectrometry, monitoring the precursor-to-product ion reaction channels: *m/z* 441→379 for delafloxacin, *m/z* 407→345 for an analog internal standard, or 446→381 for the deuterated delafloxacin internal standard. The mean accuracy was within 85% to 115% of theoretical, and the precision of the assay did not exceed a %CV of 15%.

Pharmacokinetic Analysis

Pharmacokinetic parameters were calculated by noncompartmental methods using SAS software, version 9.1 or higher (SAS Institute, Cary, North Carolina). The T_{max} and C_{max} were the observed values. The terminal elimination rate (λ_Z) 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_{0-t}, AUC_{0-12}, 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 by λ_Z. The $AUC_{0-\infty}$ was calculated as $AUC_{0-\infty} = AUC_{0-t} + AUC_{ext}$. The clearance (CL) was calculated by dividing the administered dose by the $AUC_{0-\infty}$ (single dose) or AUC_{0-12} (after 14 days of dosing). The volume of distribution (V_d) in the terminal phase was CL/λ_Z. The V_d at steady state was mean residence time divided by CL. The accumulation ratio (R_{ac}) was the ratio of the day 14 AUC_{0-12} to the day 1 AUC_{0-12}. The percentage of dose recovered as unchanged delafloxacin in urine was calculated as the total amount of delafloxacin recovered in urine (A_u) for the 24-hour or 48-hour interval after the single dose on day 1 or the 12-hour interval after the first dose on day 14 divided by the total administered dose and multiplied by 100. Renal clearance (CL_r) was A_u divided by AUC_{0-24} or AUC_{0-48} after the single dose on day 1 or A_u/AUC_{0-12} after the first dose on day 14.

Statistical Analysis

Statistical analysis was conducted using SAS software, version 9.1 or higher (SAS Institute). A dose proportionality assessment was performed on C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ using a power model. Dose proportionality was considered to be ruled out if 1 was not included in the 90% CI of the slope of a linear regression of the ln-transformed parameters. To compare the relative exposures of oral delafloxacin (450 mg) to IV delafloxacin (300 mg), a linear mixed-effect model was performed on the ln-transformed values of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. The geometric least squares mean ratio of the 2 treatments for the pharmacokinetic parameters was calculated by an antilog of the least squares mean difference of the log-transformed values. A 90% CI for the ratio was constructed as the antilog of the confidence limits of the least squares mean difference. No adjustment was made for multiplicity. Equivalence in total exposure was concluded if the 90% CI of the ratios of geometric means were entirely contained with 80% to 125% for AUC_{0-t} and $AUC_{0-\infty}$.

*Trademark: Captisol® (Ligand Technology, La Jolla, California).

Safety Analysis

Safety parameters were monitored throughout all 3 studies by physical examinations, vital signs, ECGs, laboratory evaluations, and the assessment of AEs.

RESULTS

Study Population

A summary of the demographic characteristics of the study participants for the 3 studies is presented in Table I. A total of 94 healthy men and women were enrolled across the 3 studies. Their demographic characteristics were generally consistent across studies. One volunteer in the multiple-dose study discontinued participation early because of an AE of nausea and vomiting. Two volunteers in the relative bioavailability study discontinued participation early because they tested positive for ethanol.

Pharmacokinetic Properties of Delafloxacin after Single Ascending Doses

The mean plasma concentration-time profiles after single-ascending doses (300–1200 mg) of delafloxacin are shown in Figure 1. The mean (SD) pharmacokinetic parameters for the single-ascending-dose study (300–1200 mg) are listed in Table II. The T_{max} of delafloxacin was at the end of infusion for all dose levels. The plasma concentration profiles decreased biexponentially with a mean terminal half-life of approximately 12 hours for most doses (450 mg, 600 mg, 900 mg, and 1200 mg) but ranged from 8.21 (300 mg) to 17.74 (750 mg) hours. The terminal half-life could not be determined in several participants because of the limits of the sampling schedule, the limit of quantitation, and long terminal half-life. The terminal half-life generally accounted for only a small portion of the AUC. The V_d at steady state ranged from 30.21 to 38.46 L and was dose independent. Clearance ranged 7.59 to 12.53 L/h and tended to decrease with increasing dose. Statistical analysis of dose proportionality revealed that C_{max} increased proportionally in the 300- to 1200-mg dose range, whereas AUC_{0-t} and $AUC_{0-\infty}$ increased more than proportionally in this dose range (Table III). Applying the method of Smith et al[11] to establish dose proportionality, the criterion 90% CI for the slope of the parameters for the range of evaluated doses is 0.96 to 1.14. The estimated slopes for the AUC values were completely outside the criterion 90% CI, whereas the slope for C_{max} was completely within the interval. When

Table I. Demographic characteristics of the study participants.

Characteristic	Single-Ascending-Dose IV Delafloxacin (300, 450, 600, 750, 900, 1200 mg)		Multiple-Dose IV Delafloxacin (300 mg BID for 14 days)		Single-Dose Bioavailability IV (300 mg) vs Oral (450 mg) Delafloxacin (n = 56)
	Placebo (n = 10)	Delafloxacin (n = 52)	Placebo (n = 4)	Delafloxacin (n = 8)	
Age, mean (SD) [range]	31.2 (9.65) (21–52)	37.6 (12.7) (19–64)	30.3 (7.63) (23–41)	37.8 (10.4) (18–50)	36.2 (10.9) (20–61)
Weight, mean (SD) [range]	78.8 (14.4) (60.1–100.6)	73.8 (10.6) (50.8–99.2)	72.2 (8.99) (60.4–82.0)	71.7 (10.2) (52.2–86.2)	75.3 (11.9) (52.7–97.7)
BMI, mean (SD) [range]	26.9 (3.83) (20.4–31.4)	25.9 (2.94) (19.9–31.1)	25.8 (3.12) (21.3–28.2)	25.3 (2.82) (22.1–29.6)	26.5 (3.10) (19.2–31.6)
Sex, no. (%)					
Male	6 (60.0)	29 (55.8)	2 (50.0)	5 (62.5)	28 (50.0)
Female	4 (40.0)	23 (44.2)	2 (50.0)	3 (37.5)	28 (50.0)

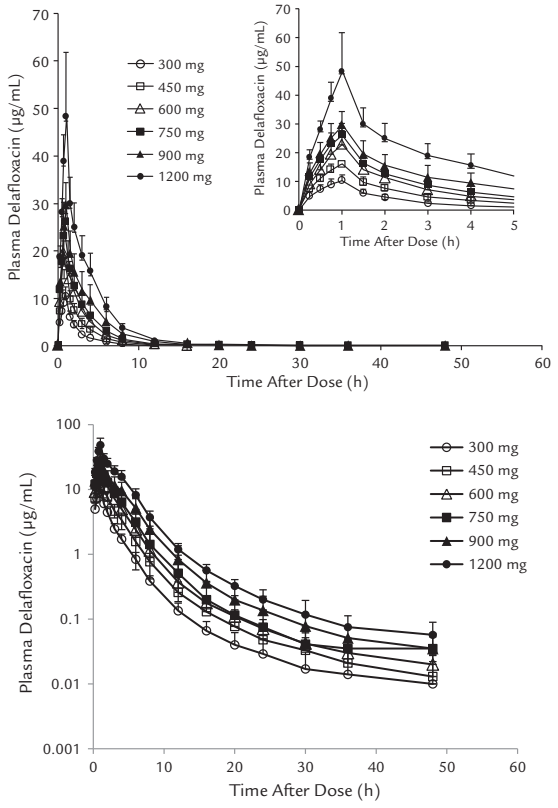

Figure 1. Mean (SD) plasma concentration-time curves of delafloxacin after single IV 1-hour infusions of 300 to 1200 mg. Top, linear plot; bottom, semilog plot.

doses increased in ratios of 1.5 (450 mg/300 mg), 2 (600 mg/300 mg), 2.5 (750 mg/300 mg), 3 (900 mg/300 mg), and 4 (1200 mg/300 mg), the corresponding means ratios for $AUC_{0-\infty}$ were approximately 1.7, 2.4, 3.0, 4.0, and 6.4, respectively. The corresponding C_{max} ratios were 1.5, 2.2, 2.5, 2.8, and 4.7, respectively. The percentage of delafloxacin recovered in the urine ranged from 30% to 40%. The CL_r decreased slightly with increasing dose at 4.98 L/h for 300 mg to 2.64 L/h for 1200 mg, respectively.

Pharmacokinetic Properties of Delafloxacin After Multiple Doses

The mean (SD) pharmacokinetic parameters after multiple 300-mg IV infusion doses of delafloxacin are listed in Table II. The pharmacokinetic parameters of delafloxacin did not change as a result of repeated dosing. The C_{max} values for delafloxacin on days 1 and 14 were 8.94 and 9.29 µg/mL, respectively. The AUC_{0-12} values for delafloxacin on days 1 and 14 were 21.8 h · µg/mL and 23.4 h · µg/mL, respectively. There was no appreciable accumulation of delafloxacin after 14 days of twice-daily dosing as indicated by a mean R_{ac} of 1.09. Mean delafloxacin CL was similar on day 1 (14.1 L/h) and day 14 (13.8 L/h). The CL_r of delafloxacin was also comparable on day 1 (5.89 L/h) and day 14 (6.69 L/h).

Absolute Bioavailability

The mean plasma concentration-time profiles of delafloxacin after single IV (300 mg) and oral (450 mg) doses are shown in Figure 2, and the pharmacokinetic parameters of delafloxacin are given in Table IV. A summary of the statistical analysis of bioequivalence of the 2 formulations is given in Table V. Equivalence in delafloxacin total exposure (AUC_{0-t} and $AUC_{0-\infty}$) after intravenous (reference) and oral (test) delafloxacin was found because the 90% CI of the ratios of geometric means was contained within the 80% to 125% interval. There was no statistically significant sequence or period effect. C_{max} was not equivalent for the intravenous and oral doses because the test-to-reference ratios were outside the 80% to 125% interval. The mean absolute bioavailability of delafloxacin was 58.8%.

Safety Profile and Tolerability

Delafloxacin was well tolerated in all 3 studies (Table VI). There were no clinically significant findings resulting from clinical laboratory assessments, vital signs, ECG results, or physical examinations in the 3 studies. In the single-ascending-dose study, a total of 16 participants (32%) reported a treatment-emergent AE, most of which were classified as gastrointestinal disorders (primarily nausea, vomiting, and diarrhea) and nervous system disorders. Most AEs were classified as mild and considered possibly related to delafloxacin. The AEs of nausea and vomiting were dose related, with few events reported at the 300-mg dose level. The 1200-mg treatment groups reported the largest number of AEs, which were primarily gastrointestinal events, with most of moderate severity and probably related to delafloxacin. In the multiple-dose study, 75% of participants in the placebo and delafloxacin groups reported a

Table II. Mean (SD) pharmacokinetic parameters of delafloxacin after a single or multiple IV 1-hour infusion to healthy volunteers.

	Delafloxacin Single IV Infusion (SBEβCD Lyophilized)						Delafloxacin Multiple IV Infusion (Cyclodextrin Solution), 300 mg BID[*]	
Pharmacokinetic Parameter	300 mg (n = 12)	450 mg (n = 8)	600 mg (n = 8)	750 mg (n = 8)	900 mg (n = 8)	1200 mg (n = 8)	Day 1 (n = 8)	Day 14 (n = 7)
C_{max}, μg/mL	10.4 (1.95)	16.1 (2.01)	23.0 (4.82)	26.2 (3.94)	29.7 (4.67)	49.1 (12.38)	8.94 (4.54)	9.29 (1.83)
T_{max}, h[†]	1.00 (0.97–1.08)	1.00 (1.00–1.00)	1.02 (1.00–1.03)	1.00 (1.00–1.15)	1.00 (1.00–1.03)	1.02 (0.80–1.05)		
AUC_{0-t}, μg · h/mL	24.7 (4.89)	42.6 (7.26)	61.5 (15.0)	74.0 (20.1)	98.1 (28.3)	156 (27.8)		
$AUC_{0-\infty}$, μg · h/mL	24.8 (4.87)[‡]	42.9 (7.24)	59.0 (13.7)[‡]	74.4 (3.49)[‡]	99.3 (26.0)[‡]	160 (18.5)[‡]	22.1 (4.45)[§]	ND
AUC_{12} (μg · h/mL)[§]							21.8 (4.54)	23.4 (6.90)
$t_{½}$, h	8.21 (2.72)[‡]	12.5 (5.46)	11.9 (5.32)[‡]	17.7 (2.40)[‡]	11.6 (7.79)[‡]	11.7 (4.00)[‡]		
CL, L/h	12.53 (2.64)[‡]	10.8 (1.91)	10.6 (2.36)[‡]	10.1 (0.48)[‡]	9.65 (2.80)[‡]	7.59 (0.96)[‡]	14.1 (2.81)[§]	ND
V_{ss}, L	34.2 (6.73)[‡]	36.6 (9.57)	38.5 (12.6)[‡]	32.9 (4.15)[‡]	36.4 (6.71)[‡]	30.2 (4.29)[‡]		
V_Z, L	146.1 (50.3)[‡]	198 (110)	194 (128)[‡]	257 (23.5)[‡]	148 (75.5)[‡]	131 (58.1)[‡]		
Ae_{0-48}, mg	117 (26.8)	165 (34.4)	226 (29.0)	235 (65.5)	304 (68.1)	410 (100)		
$Fe\%_{00-48}$, %	38.9 (8.92)	36.7 (7.65)	37.7 (4.83)	31.4 (8.73)	33.8 (7.57)	34.1 (8.36)		
R_{ac}							ND	1.09 (0.123)
CL_r, L/h	4.98 (1.66)	4.04 (1.39)	3.95 (1.36)	3.24 (0.80)	3.47 (1.76)	2.64 (0.50)	5.89 (1.55)	6.69 (2.19)

ND = not determined; SBEβCD = sulfobutyl-ether-β-cyclodextrin.

[*]On day 1, a single IV dose of 300 mg of delafloxacin (1-hour infusion) was given at 0 hour. On days 2 through 14, a 300-mg dose of delafloxacin (IV 1-hour infusion) was administered BID at 0 and 12 hours.

[†]Median (range).

[‡]n = 9 for the 300-mg group, n = 7 for the 600-mg group, n = 3 for the 750-mg group, and n = 6 for the 900-mg and 1200-mg groups.

[§]n = 7.

Table III. Statistical analysis of dose proportionality.*

Parameter	Estimated Slope (90% CI) for Ln (Dose) for the Delafloxacin 300- to 1200-mg Group	*P* (Slope = 1)
AUC_{0-t}	1.2790 (1.1700–1.3880)	<0.0001
$AUC_{0-\infty}$	1.3064 (1.1969–1.4158)	<0.0001
C_{max}	1.0520 (0.9615–1.1426)	0.3402

*The power model, ln(parameter) = a + b * ln(dose) + error, was used to estimate the slope, corresponding 90% CI, and the *P* value testing dose proportionality (b = 1).

treatment-emergent AE. One participant treated with delafloxacin discontinued participation in the study because of an AE of nausea and vomiting considered moderate in severity. In the bioavailability study, a total of 11 participants (19.6%) had an AE. The most frequently reported AEs were headache (5.4%) and diarrhea (3.6%). Most AEs were mild and resolved by the end of the study.

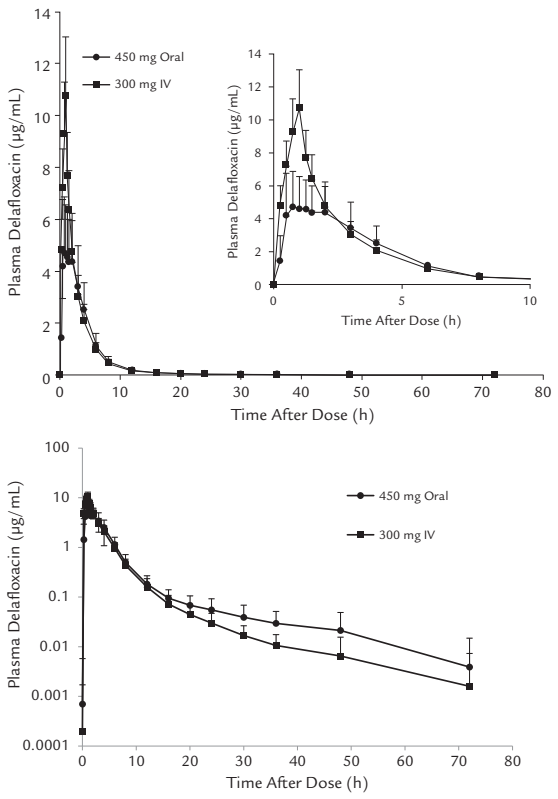

Figure 2. Mean (SD) plasma concentration-time curves of delafloxacin after a single IV 1-hour infusion (300-mg) and single oral (450-mg) administration to healthy volunteers. Top, linear plot; bottom, semilog plot.

DISCUSSION

The increase in hospitalization due to ABSSSIs reinforces the need for new treatment options.[12,13] Limited intravenous and oral treatment options for ABSSSIs that provide broad-spectrum coverage are limited because of the increasing prevalence of resistant pathogens, including MRSA and toxic effects associated with the current available treatments.[14,15] Delafloxacin is an investigational anionic fluoroquinolone antibiotic that has efficacy for the treatment of ABSSSI. Both IV (300 mg) and oral (450 mg) formulations of delafloxacin are currently in Phase III development for the treatment of ABSSSIs.

The present study reports on the safety profile, tolerability, and pharmacokinetic parameters of IV delafloxacin from 3 studies in healthy volunteers. Delafloxacin has a good tolerability profile when administered by intravenous infusion. In the single-ascending-dose study, the most common AE was gastrointestinal, which appeared to be dose related. Most of the AEs were mild in severity. There were no clinically significant findings from clinical laboratory data, vital signs, or physical examinations. These results are consistent with the safety findings from 2 Phase II studies of ABSSSIs in which IV doses of 300-mg delafloxacin were found to be well tolerated, with gastrointestinal AEs the most common AE.[6,7] There were no clinical significant ECG results, including no

Table IV. Mean (SD) pharmacokinetic parameters of delafloxacin after a single IV 1-hour infusion or a single oral dose to healthy volunteers.

Pharmacokinetic Parameter	Delafloxacin 450-mg Tablet (n = 55)	Delafloxacin 300-mg IV Infusion (n = 55)
T_{max}, h[*]	0.817 (0.50–4.00)	1.00 (0.75–1.13)
C_{max}, μg/mL	6.12 (1.96)	10.7 (2.29)
AUC_{0-t}, μg · h/mL	23.3 (7.00)	26.9 (5.78)
$AUC_{0-\infty}$, μg · h/mL[†]	24.2 (6.45)	26.7 (6.03)
F[‡]	58.8 (10.5)[§]	

[*]Median (range).
[†]n = 42 for the oral tablet and n = 49 for the IV infusion.
[‡]F was calculated for each participants as ($AUC_{0-\infty}$ after oral)(IV dose)/($AUC_{0-\infty}$ after IV)(oral dose).
[§]n = 37.

effect on prolongation of the QT interval in these Phase I studies, which is consistent with a thorough QTc study that found no risk for prolongation of the QTc interval with a delafloxacin supratherapeutic dose.[9]

Delafloxacin concentrations decreased in plasma in a biexponential manner with a terminal half-life of approximately 12 hours at most dose levels. However, examination of the plasma profiles suggests the terminal phase would contribute little to the accumulation of the drug with BID dosing. As expected, after twice-daily dosing there was minimal accumulation of delafloxacin at steady state (mean $R_{ac} = 1.09$). Delafloxacin was well distributed with a V_d at steady state of approximately 35 L, which is similar to that of total body water. Delafloxacin peak exposure (C_{max}) increased in a dose-proportional manner in the 300- to 1200-mg dose range evaluated, whereas total exposure (AUC) increased more than proportionally with dose (increasing 6.4-fold over the 4-fold dose range studied). The reasons for the lack of proportionality were not investigated but could be caused by saturation of an elimination pathway. After intravenous administration, most radioactivity was excreted in urine (65%), with 28% excreted in feces.[10] The radioactivity in feces

Table V. Statistical analysis of IV infusion (300 mg) and oral (450 mg) delafloxacin pharmacokinetic parameters.

Pharmacokinetic Parameter	N	Geometric Least Squares Mean (90% CI)	Ratio Geometric Least Squares Mean (Oral/IV), % (90% CI)
$AUC_{0-\infty}$, μg · h/mL			
Oral	42	22.97 (21.61–24.41)	87.68 (83.56–92.00)
IV	49	26.20 (24.71–27.78)	
AUC_{0-t}, μg · h/mL			
Oral	55	22.24 (20.99–23.57)	84.45 (80.90–88.15)
IV	55	26.34 (24.85–27.91)	
C_{max}, μg/mL			
Oral	55	5.80 (5.44–6.17)	55.16 (51.50–59.08)
IV	55	10.51 (9.87–11.19)	

Table VI. Summary of treatment-emergent adverse events regardless of causality.

	No. (%) of Participants by Treatment Group										
	Single Ascending IV Dose Study (Delafloxacin Dose)							Multiple IV Dose Study (Delafloxacin Dose)		Bioavailability IV vs Oral Study (Delafloxacin Dose)	
System Organ Class	Placebo	300 mg (n = 12)	450 mg (n = 8)	600 mg (n = 8)	750 mg (n = 8)	900 mg (n = 8)	1200 mg (n = 8)	Placebo (n = 4)	300 mg (n = 8)	300 mg IV (n = 55)	450 mg Oral (n = 55)
Gastrointestinal disorders	1 (10.0)	1 (8.3)	0	0	2 (25.0)	3 (37.5)	7 (87.5)	3 (75.0)	5 (62.5)	2 (3.6)	2 (3.6)
Nausea	1 (10.0)	0	0	0	2 (25.0)	3 (37.5)	4 (50.0)	1 (25.0)	3 (37.5)	1 (1.8)	0
Vomiting	0	0	0	0	0	0	6 (75.0)	0	0	1 (1.8)	
Diarrhea	0	0	0	0	1 (12.5)	1 (12.5)	2 (25.0)	0	0	0	2 (3.6)
Abdominal pain	0	0	0	0	1 (12.5)	0	0	2 (50.0)	4 (50.0)	0	0
Retching	0	0	0	0	0	0	1 (12.5)	0	0	0	0
Abdominal distension	0	1 (8.3)	0	0	0	0	0	0	0	0	0
Abdominal discomfort	0	0	0	0	0	0	0	0	0	0	1 (1.8)
Infrequent bowel movements	0	0	0	0	0	0	0	0	0	1 (1.8)	0
Nervous system disorders	1 (10.0)	1 (8.3)	0	0	1 (12.5)	2 (25.0)	1 (12.5)	3 (75.0)	4 (50.0)	3 (5.5)	1 (1.8)
Headache	1 (10.0)	0	0	0	0	2 (25.0)	0	1 (25.0)	2 (25.0)	2 (3.6)	1 (1.8)
Dizziness	0	1 (8.3)	0	0	0	1 (12.5)	1 (12.5)	2 (50.0)	3 (37.5)	1 (1.8)	0
Presyncope	0	0	0	0	1 (12.5)	0	0	0	0	0	0
Somnolence	1 (10.0)	0	0	0	0	0	0	0	0	0	0
Sinus headache	0	0	0	0	0	0	0	1 (12.5)	0	1 (1.8)	0
Paraesthesia	0	0	0	0	0	0	0	0	1 (12.5)	0	0
Dysgeusia	0	0	0	0	0	0	0	0	0	1 (1.8)	0

(continued)

Table VI. (continued).

	No. (%) of Participants by Treatment Group										
	Single Ascending IV Dose Study (Delafloxacin Dose)							Multiple IV Dose Study (Delafloxacin Dose)		Bioavailability IV vs Oral Study (Delafloxacin Dose)	
System Organ Class	Placebo	300 mg (n = 12)	450 mg (n = 8)	600 mg (n = 8)	750 mg (n = 8)	900 mg (n = 8)	1200 mg (n = 8)	Placebo (n = 4)	300 mg (n = 8)	300 mg IV (n = 55)	450 mg Oral (n = 55)
General disorders and administration site conditions	1 (10.0)	0	0	0	0	1 (12.5)	1 (12.5)	3 (75.0)	3 (37.5)		1 (1.8)
Feeling hot	0	0	0	0	0	1 (12.5)	1 (12.5)	0	1 (12.5)	0	0
Asthenia	0	0	0	0	0	1 (12.5)	0	1 (12.5)	0	0	0
Thirst	0	0	0	0	0	1 (12.5)	0	0	0	0	0
Vessel puncture site swelling	1 (10.0)	0	0	0	0	0	0	0	1 (12.5)	0	0
Injection site pain	0	0	0	0	0	0	0	1 (25.0)	3 (37.5)	0	0
Feeling cold	0	0	0	0	0	0	0	0	1 (12.5)	0	0
Injection site inflammation	0	0	0	0	0	0	0	0	1 (12.5)	0	0
Injection site reaction	0	0	0	0	0	0	0	1 (12.5)	0	0	0
Edema peripheral	0	0	0	0	0	0	0	1 (12.5)	0	0	0
Energy decreased	0	0	0	0	0	0	0	0	0	0	1 (1.8)
Respiratory, thoracic and mediastinal disorders	0	1 (8.3)	0	0	0	1 (12.5)	1 (12.5)	0	0	0	0
Nasal congestion	0	1 (8.3)	0	0	0	1 (12.5)	0	0	0	0	0
Rhinorrhea	0	0	0	0	0	0	1 (12.5)	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	0	1 (12.5)	1 (12.5)	1 (25.0)	3 (37.5)	1 (1.8)	0

(continued)

Table VI. (continued).

System Organ Class	No. (%) of Participants by Treatment Group										
	Single Ascending IV Dose Study (Delafloxacin Dose)							Multiple IV Dose Study (Delafloxacin Dose)		Bioavailability IV vs Oral Study (Delafloxacin Dose)	
	Placebo	300 mg (n = 12)	450 mg (n = 8)	600 mg (n = 8)	750 mg (n = 8)	900 mg (n = 8)	1200 mg (n = 8)	Placebo (n = 4)	300 mg (n = 8)	300 mg IV (n = 55)	450 mg Oral (n = 55)
Hyperhidrosis	0	0	0	0	0	1 (12.5)	0	1 (25.0)	0	0	0
Pruritus	0	0	0	0	0	0	1 (12.5)	0	1 (12.5)	1 (1.8)	0
Dermatitis contact	0	0	0	0	0	0	0	0	2 (25.0)	0	0
Cold sweat	0	0	0	0	0	0	0	1 (12.5)	0	0	0
Dermatitis	0	0	0	0	0	0	0	0	1 (12.5)	0	0
Infections and infestations	0	1 (8.3)	0	0	0	0	0	0	0	1 (1.8)	0
Vulvovaginal candidiasis	0	1 (8.3)	0	0	0	0	0	0	0	1 (1.8)	0
Folliculitis	0	0	0	0	0	0	0	0	1 (12.5)	0	0
Eye disorders	0	0	0	0	0	0	0	1 (25.0)	0	0	0
Eye irritation	0	0	0	0	0	0	0	1 (25.0)	0	0	0
Reproductive system and breast disorders	0	0	0	0	0	0	0	0	1 (12.5)	0	0
Uterine hemorrhage	0	0	0	0	0	0	0	0	1 (12.5)	0	0
Vulvovaginal discomfort	0	0	0	0	0	0	0	0	1 (12.5)	0	0
Musculoskeletal and connective tissue disorders	0	0	0	0	0	0	0	0	0	1 (1.8)	0
Myalgia	0	0	0	0	0	0	0	0	0	1 (1.8)	0

was unchanged delafloxacin, whereas the radioactivity in urine was either unchanged delafloxacin (34%–47% of the dose) or delafloxacin glucuronide (15%–22% of the dose). The metabolism of delafloxacin to glucuronides is primarily mediated by UGT1A1 and UGT1A3 (data on file at Melinta Therapeutics). In vitro, delafloxacin is not a substrate of transporters OAT1, OAT3, OCT1, OCT2, OATP1B1, or OATP1B3, but it is a probable substrate of breast cancer resistance protein and possibly a substrate of P-glycoprotein (data on file at Melinta Therapeutics).

The present results indicate that CL_r represents approximately 35% to 40% of the total delafloxacin clearance. These results are consistent with a radiolabeled mass-balance study of intravenous [^{14}C]delafloxacin, which found that most of the radioactivity excreted in urine was unchanged delafloxacin.[10] Delafloxacin clearance is reduced in patients with renal impairment and in patients with end-stage renal disease undergoing dialysis.[16]

Delafloxacin was well absorbed after administration of the 450-mg tablet, with a mean absolute bioavailability of 58.8%. The 450-mg oral dose was developed to match the exposure of the 300-mg IV dosage. The total exposure (AUC_{0-t} or $AUC_{0-\infty}$) to delafloxacin was equivalent after IV (300 mg) and oral (450 mg) administration. The peak exposure was not equivalent for the 2 formulations, with the C_{max} being lower for the tablet formulation. Lack of equivalence for peak exposure is not considered clinically important because the efficacy of delafloxacin is best correlated with the AUC/MIC ratio, similarly to other fluoroquinolones.[17] A lower C_{max} with the oral formulation may be an advantage because higher doses exposures have been associated with more gastrointestinal AEs.[18] Equivalence of delafloxacin total exposure will allow for maintaining efficacious exposures with the switch between the intravenous and oral formulations. The ability to change from intravenous to oral may reduce the duration of hospitalization and the need for indwelling catheters, thus reducing the cost of treatment for some patients.

CONCLUSIONS

In summary, the pharmacokinetic parameters of delafloxacin after IV (300 mg) and oral (450 mg) administration are comparable, supporting that a switch between the 2 formulations would be acceptable. The results reveal suitable pharmacokinetic parameters and good tolerability for delafloxacin when given twice daily as 300-mg intravenous 1-hour infusions. The pharmacokinetic parameters of IV delafloxacin suggest steady state should be achieved within 2 to 3 days, and, as expected, minimal accumulation was observed after twice-daily dosing in a 14-day study. Renal elimination of unchanged delafloxacin accounts for approximately 30% to 40% of the total clearance after intravenous administration. Intravenous delafloxacin was well tolerated in healthy volunteers after single- and multiple-dose administration.

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CONFLICTS OF INTEREST

Melinta Therapeutics contributed to the study design and the collection, analysis, and interpretation of data. Sue Cammarata, Randall Hoover, Laura Lawrence, and Eugene Sun are employees of Melinta Therapeutics. Susan K. Paulson was compensated for writing of the manuscript. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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