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Pharmacokinetics (PK) of Delafloxacin (DLX) in Patients with Varying Degrees of Renal Impairment

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Abstract

Background and Objective
Delafloxacin, an investigational fluoroquinolone, has activity against Gram-positive organisms including methicillin-resistant *S. aureus* (MRSA), and against fluoroquinolone-susceptible Gram-negative organisms. This study was conducted to determine the PK of DLX after single intravenous (IV) infusion or oral doses in subjects with normal or impaired renal function.

Methods
This was an open-label, parallel group, crossover study. Subjects with normal renal function (eGFR: ≥80 mL/min/1.73 m^2); mild, moderate, or severe renal impairment (eGFR: 50 to 79; 30 to 49; 15 to 29 mL/min/1.73 m^2, respectively); or end-stage renal disease (ESRD) undergoing hemodialysis were enrolled (n = 8 to 9 per group). Subjects in the normal through severe categories received a 1-hr IV infusion of 300 mg of DLX, an infusion of placebo, and an oral dose of 400 mg of DLX, in three periods separated by ≥14 day washouts. ESRD patients received 1-hr IV infusions of 300 mg of DLX immediately before or after hemodialysis, in two periods separated by ≥14 day washouts. Blood, urine, and dialysate samples were collected as appropriate. Study samples were analyzed for DLX using validated LC-MS/MS methods. PK parameters were calculated using noncompartmental methods.

Results
DLX clearance (total and renal) decreased with decreasing renal function, with a corresponding increase in AUC. After IV administration, mean (CV%) total clearance decreased from 13.7 (19.1) to 6.59 (31.5) L/hr in normal and severe renal subjects, respectively, and mean (CV%) AUC_{inf} increased from 22.6 (20.0) to 51.1 (40.9) hr*ug/mL, respectively. Mean (CV%) renal clearance as determined by urinary excretion decreased from 6.03 to 0.40 L/hr in normal and severe renal subjects, respectively. Total clearance exhibited a linear relationship to eGFR. Similar observations were made after oral administration of DLX. In ESRD patients, a mean of 19% of an IV dose of DLX was removed by 4-hr hemodialysis.

Conclusion
Intravenous infusion of 300 mg, and oral dosing of 400 mg of DLX was well tolerated in subjects with renal insufficiency. The results indicate that renal insufficiency has an effect on the clearance of delafloxacin, consistent with its known elimination pathways.

Introduction

Delafloxacin (DLX, RX-3341) is an investigational fluoroquinolone that is active against Gram-positive and –negative bacteria, including methicillin- and quinolone-resistant strains of *Staphylococcus aureus* (MRSA, QRSA). DLX is eliminated by both renal and hepatic pathways. This study was conducted to determine the effects of renal impairment on the pharmacokinetics of DLX after single intravenous (IV) infusion or oral doses.

Methods

Study Design
This was a phase I, open-label, parallel-group crossover study to assess the effect of renal impairment on the single-dose pharmacokinetics and safety of oral and IV delafloxacin and IV placebo. Subjects with normal renal function; mild, moderate, or severe renal impairment; or end-stage renal disease undergoing hemodialysis were enrolled. Subjects with normal renal function were matched to the renally impaired subjects in terms of gender distribution, mean age (±10 years), and mean BMI (±20%). Subjects in the normal through severe categories received a 1-hr IV infusion of 300 mg of DLX, an infusion of placebo, and an oral dose of 400 mg of DLX, in three periods separated by ≥14 day washouts. ESRD patients received 1-hr IV infusions of 300 mg of DLX immediately before or after hemodialysis, in two periods separated by ≥14 day washouts.

Table 1. Subject Demographics

	Normal (N=9)	Mild Impairment (N=8)	Moderate Impairment (N=8)	Severe Impairment (N=9)	ESRD (N=8)	Total (N=42)
Sex (n, Males/Females)	4/5	5/3	5/3	4/5	5/3	23/19
Race (n, Caucasian/African-American/Other)	8/1/0	4/4/0	2/5/1	4/4/1	3/5/0	21/19/2
Age (yr) (Mean ± SD)	51.6 ± 4.0	55.9 ± 9.8	56.8 ± 9.3	53.8 ± 8.6	51.0 ± 18.8	53.7 ± 10.7
Range	46 - 59	42 - 70	42 - 70	40 - 66	26 - 71	26 - 71
Weight (kg) (Mean ± SD)	83.7 ± 12.9	94.0 ± 14.8	98.2 ± 25.0	91.9 ± 18.1	78.0 ± 24.1	89.1 ± 19.8
Range	66.3 - 107.9	71.8 - 117.1	68.4 - 140.4	64.0 - 116.2	45.9 - 111.0	45.9 - 140.4
Height (cm) (Mean ± SD)	174 ± 13	174 ± 8	175 ± 9	170 ± 9	168 ± 11	172 ± 10
Range	160 - 198	161 - 183	161 - 187	159 - 183	152 - 184	152 - 198
BMI (kg/m^2) (Mean ± SD)	27.5 ± 2.1	31 ± 3.4	31.8 ± 6.8	31.7 ± 5.3	27.1 ± 5.7	29.8 ± 5.1
Range	25.0 - 31.7	27.8 - 37.8	23.6 - 40.3	23.9 - 38.4	18.4 - 36.5	18.4 - 40.3
eGFR (mL/min/1.73 m^2) (Mean ± SD)	91.9 ± 11.4	62.8 ± 7.8	38.6 ± 4.9	22.3 ± 6.2		54.1 ± 28.3
Range	83 - 119	53-78	31 - 45	29-Sep		9 - 119

Pharmacokinetic Sampling
For the IV treatments, blood for plasma samples was collected before dosing and at 0.33, 0.66, 1 (end of infusion), 1.083, 1.167, 1.33, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours after the start of the infusion. ESRD subjects had an additional blood sample collected between 65 and 69 hours after dosing in Period 2 only. PK samples were collected into a tube containing K_2EDTA. For the oral treatment, blood for plasma samples was collected before dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 20, 24, 30, 36, and 48 hours after dosing.
For all subjects, an additional blood sample was collected before dosing in Period 1 for the determination of plasma protein binding of delafloxacin.

Bioanalysis
Delafloxacin in plasma, urine, and dialysate were quantitated using validated LC-MS/MS methods. Samples were processed by liquid-liquid extraction using 50:50 ethyl acetate:hexane. The processed samples were analyzed by an LC-MS/MS method with calibration ranges of 5 to 2500 ng/mL (plasma and dialysate) or 50-10,000 ng/mL (urine).

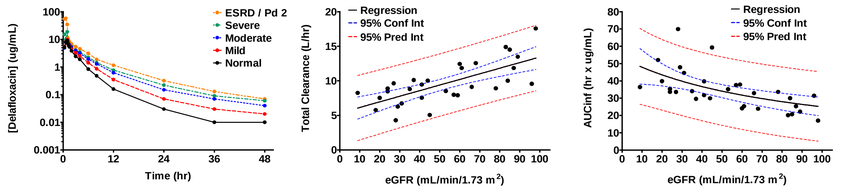
Pharmacokinetic Analysis
Plasma concentration data for delafloxacin were analyzed by noncompartmental methods using Phoenix WinNonlin, Version 6.2.1. Pharmacokinetic parameters determined included C_{max}, T_{max}, AUC_{inf}, $T_{1/2}$, CLtot(/F), and CLr(/F). Graphics and regressions were prepared using GraphPad Prism Version 5.01. Regressions were performed only with data from the normal to severe categories. Some data was excluded from regression analysis due to pharmacokinetic implausibility.

Results

Pharmacokinetics
After intravenous infusion of 300 mg over 1 hr, the AUC of DLX increased with greater degrees of renal impairment (Figure 1, Table 1). In normal subjects, mean AUC_{inf} was 22.6 hr*ug/mL, and increased to 31.3, 38.4, 51.1, and 97.5 hr*ug/mL in mild, moderate, severe, and post-dialysis ESRD categories, respectively. Compared to the normal category, the difference in AUC_{inf} in mild subjects was not significant, but for all other categories the differences were significant (90% CI). Total and renal clearance decreased with increasing renal impairment. Nonrenal clearance and C_{max} were essentially unchanged with increasing renal impairment (data not shown).

Linear regression of CLtot versus eGFR (normal through severe categories) produced the following relationship: CLtot = 5.34 + 0.081 * eGFR. The slope of the relationship was statistically significant at p < 0.0001.

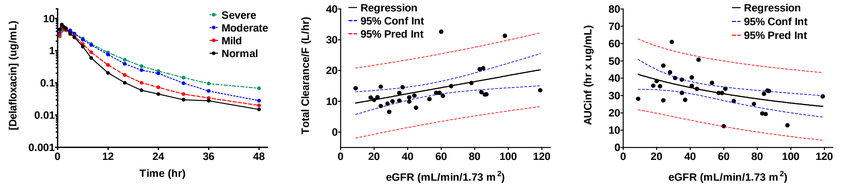
Figure 1. IV Infusion, 300 mg over 1 hr: Plasma Concentrations (Left), Clearance (Center), AUCinf (Right)



After oral administration of 400 mg, the AUC of DLX increased with greater degrees of renal impairment (Figure 2, Table 2). In normal subjects, mean AUC_{inf} was 25.4 hr*ug/mL, and increased to 28.3, 37.3, and 39.5 hr*ug/mL in mild, moderate, and severe categories, respectively. Compared to the normal category, the difference in AUC_{inf} in mild subjects was not significant, but for all other categories the differences were significant. Total and renal clearance (/F) decreased with increasing renal impairment. Nonrenal clearance (/F) and C_{max} were essentially unchanged with increasing renal impairment (data not shown).

Linear regression of CLtot/F versus eGFR (normal through severe categories) produced the following relationship: CLtot/F = 8.53 + 0.099 * eGFR. The slope of the relationship was statistically significant at p < 0.001.

Figure 2. Oral Administration, 400 mg: Plasma Concentrations (Left), Clearance/F (Center), AUCinf (Right)



In ESRD subjects, when 300 mg DLX was given by IV infusion immediately prior to a hemodialysis session, mean AUC_{inf} was 84.3 hr*ug/mL compared to 97.5 hr*ug/mL when the infusion was given immediately after the end of a hemodialysis session (Table 1). Analysis of dialysate fluid indicated the mean (CV%) percent of an IV dose removed by hemodialysis was 19.2 (18.9) percent (data not shown).

Plasma protein binding showed a tendency to decrease with increasing renal impairment (data not shown), although the relationship barely achieved significance (p = 0.049). Over the range of eGFR studied, the predicted percent unbound increased from 15.1% at an eGFR of 119 mL/min/1.73 m^2 to 19.6% at an eGFR of 9 mL/min/1.73 m^2.

Proposed Dosing Adjustment
Taking into consideration the effects of renal impairment on DLX clearance and the prediction intervals around the AUC exposure data, a proposed dosing adjustment for severely impaired patients is to administer 200 mg by IV infusion, bid, instead of 300 mg, bid.

Table 2. PK Parameters after IV Infusion

	Normal	Mild Impairment	Moderate Impairment	Severe Impairment	ESRD Pre-Dialysis	ESRD Post-Dialysis
Cmax (ug/mL) (Mean ± SD)	9.28 ± 2.35	9.80 ± 1.09	9.86 ± 2.53	19.5 ± 27.3	54.4 ± 124.3	59.8 ± 134.7
Range	6.77 - 13.6	8.36 - 11.4	7.48 - 13.9	7.37 - 87.0	5.65 - 362	6.23 - 393
n	8	8	8	8	8	8
T1/2 (hr) (Mean ± SD)	9.28 ± 4.33	10.7 ± 2.45	8.90 ± 2.98	14.2 ± 6.02	10.6 ± 5.01	15.0 ± 2.15
Range	4.20 - 16.1	8.05 - 15.6	4.97 - 14.7	8.05 - 25.1	6.17 - 22.0	11.6 - 18.9
n	6	8	7	8	8	8
AUCinf (hr*ug/mL) (Mean ± SD)	22.6 ± 4.5	31.3 ± 6.0	38.4 ± 10.7	51.1 ± 20.9	84.3 ± 100.5	97.5 ± 101.6
Range	17.1 - 30.0	23.9 - 37.9	29.6 - 59.3	33.7 - 93.5	19.0 - 327	28.0 - 340
n	6	8	7	8	8	8
CLtot (L/hr) (Mean ± SD)	13.7 ± 2.62	9.92 ± 2.01	8.25 ± 1.89	6.59 ± 2.07	6.58 ± 4.35	5.09 ± 2.94
Range	10.0 - 17.6	7.92 - 12.6	5.06 - 10.1	3.21 - 8.90	0.92 - 15.8	0.88 - 10.7
n	6	8	7	8	8	8
CLr (L/hr) (Mean ± SD)	6.03 ± 1.62	2.96 ± 2.15	1.30 ± 0.64	0.40 ± 0.36	--	--
Range	3.13 - 8.31	0.39 - 6.99	0.92 - 2.85	0.08 - 1.02	--	--
n	8	8	8	8	3	2

Table 3. PK Parameters after Oral Administration

	Normal	Mild Impairment	Moderate Impairment	Severe Impairment
Cmax (ug/mL) (Mean ± SD)	7.16 ± 2.50	5.67 ± 1.94	6.00 ± 1.78	5.35 ± 1.33
Range	3.06 - 10.4	3.36 - 9.40	3.09 - 8.37	3.43 - 8.02
n	8	8	8	8
T1/2 (hr) (Mean ± SD)	15.4 ± 6.66	12.5 ± 2.73	10.5 ± 4.24	15.5 ± 5.23
Range	5.68 - 25.5	9.86 - 17.7	5.44 - 19.2	10.1 - 24.0
n	7	7	8	8
AUCinf (hr*ug/mL) (Mean ± SD)	25.4 ± 8.01	28.3 ± 8.18	37.3 ± 7.03	39.5 ± 11.0
Range	12.8 - 32.8	12.3 - 37.3	27.4 - 50.7	27.2 - 60.9
n	7	7	8	8
Cltot/F (L/hr) (Mean ± SD)	17.6 ± 7.08	13.8 ± 9.70	11.0 ± 2.03	10.8 ± 2.77
Range	12.2 - 31.3	14.9 - 32.6	7.89 - 14.6	6.57 - 14.7
n	7	7	8	8
CLr/F (L/hr) (Mean ± SD)	5.09 ± 2.35	2.95 ± 1.60	1.03 ± 0.59	0.29 ± 0.12
Range	2.58 - 8.50	0.89 - 5.93	0.30 - 2.07	0.13 - 044
n	8	8	8	8

Conclusions

- Delafloxacin exposure increases with greater degrees of renal impairment, consistent with a reduction in renal clearance and consistent with the known elimination pathways for delafloxacin.
- Nonrenal clearance and C_{max} were not significantly affected by renal impairment.
- Hemodialysis removed a mean of about 19% of an IV dose of delafloxacin.
- A proposed dosing adjustment for severely impaired patients is to administer 200 mg by IV infusion, bid, instead of 300 mg.