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Pharmacokinetics / Pharmacodynamics of Finafloxacin in the Murine Thigh Infection Model with *S. aureus* and *E. coli*

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Abstract

Background: Finafloxacin (FIN), a novel fluoroquinolone (FQ) in clinical development, has the unique property of being activated under acidic conditions, unlike other marketed FQs. Since local acidic environments are a hallmark of bacterial infection, FIN may have an advantage over existing agents in treating these infections. This study was performed to determine the PK/PD parameter that best correlates to FIN efficacy. **Methods:** MICs for FIN and other FQs were determined at pH 5, 6 and 7.2. Female CD-1 mice were rendered neutropenic by IP injection of Cytoxan (150/100 mg/kg at days -4/-1 pre-infection). Infection was established by injection of 10^6 CFU of and MSSA or *E. coli* (Ec) strain in the right thigh. Dose fractionation studies (q24h, q12h and q6h) were performed from 0.25 - 150 mg/kg SC. All thighs were removed 26 hrs post-infection and processed for CFU counts. FIN was administered SC from 1 to 100 mg/kg to determine PK parameters (C_{max}, AUC, T>MIC) in neutropenic, thigh-infected animals. The dose vs. change in log CFU/thigh relationship vs. untreated controls was determined and related to the PK parameters at each dose. **Results:** FIN was more active than the other FQs tested at pH5. The static dose for both the MSSA and Ec was 10.7 mg/kg. The correlation coefficients of the PD parameters to efficacy in the thigh model for the 24 hr AUC/MIC, C_{max}/MIC and %T>MIC were 90, 79 and 57% for MSSA and 89, 77 and 67% for Ec, respectively. The 24 hr total AUC/MIC (pH 7.2) ratio necessary to achieve a static effect was 132.5 for the MSSA and 88.1 for the Ec. The corresponding C_{max}/MIC (pH 7.2) ratio for the static effect was 30.9 for the MSSA and 22.4 for the Ec. **Conclusion:** The efficacy of FIN in the neutropenic thigh model, for both MSSA and *E. coli* correlated best to the AUC/MIC and further investigations are warranted to determine the effect of pH at the site of infection on the magnitude of this parameter.

Introduction

Finafloxacin is a novel member of the fluoroquinolone class of antibiotics with a new pH activated profile offering therapeutic potential for severe and difficult to treat bacterial infections. Some of the characteristics of finafloxacin which set it aside from other members of the fluoroquinolone (FQ) class can be summarized as follows: pH activation and activity under infection relevant conditions; more active than other marketed FQs against the growth / physiological forms of bacteria which cause the most serious and recurrent infections; an all inclusive spectrum of activity that covers Gram positive, Gram negative, anaerobic and atypical pathogens; more effective than the classical FQs over a range of sepsis, cSSSI, RTI, UTI and IAI infection models and safety, finafloxacin has an outstanding safety profile compared to other fluoroquinolones. The current study was performed to determine the PK/PD parameter that is most predictive for the efficacy of finafloxacin.

Methods and Materials

Mice: Female 5 - 6 wk old CD-1 mice (18-22 gm) rendered neutropenic by IP injection of Cytoxan (cyclophosphamide) 150 mg/kg (-4 days) and 100 mg/kg (-1 day) pre-infection.

Thigh Infection: A fresh overnight culture of a *S. aureus* and *E. coli* strains diluted to approx. 2 x 10^6 CFU/mL and 0.1 mL injected ($5x10^5$ final CFU) IM into the thighs of the pre-treated mice.

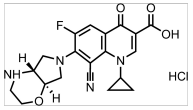
MICs: MICs for FIN at different pH were determined by microbroth dilution in accordance with CLSI guidelines.

PK: FIN was administered SC at 1 – 100 mg/kg in order to determine PK parameters (Cmax, AUC, T>MIC) and their relationship to administered dose. PK was performed in neutropenic, *S. aureus* thigh-infected animals to best predict compound levels in the efficacy studies.

Dose Ranging Study: An initial dose-ranging study (single dose at +1.5 hrs post-infection) was performed over a wide range (0.25 – 150 mg/kg) in *S. aureus* thigh-infected animals in order to determine the defined range that will be used in the dose fractionation studies.

Dose Fractionation: FIN was administered by the same route used for the PK and dose-ranging study at up to 8 different total daily doses (selected from the dose ranging studies and covering a range from maximal to the no-antibacterial effect level). Each total dose was given at 3 different regimens; q24hr, q12hr and q6hr. Efficacy in the thigh infection model was compared to calculated PK parameters at each of the dose fractionations in order to determine the PK/PD parameter that is most predictive of efficacy.

Panel 1: Chemical Structure of Finafloxacin



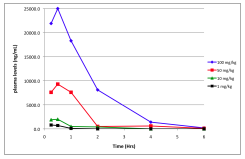
(-)-8-cyano-1-cyclopropyl-6-fluoro-7-[(4a*S*,7a*S*)-hexahydropyrrolo[3,4-*b*]-1,4-oxazin-6 (2*H*)-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylc acid hydrochloride

Panel 2: Minimum Inhibitory Concentration (MICs) of Finafloxacin and Other Fluoroquinolones

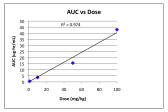
	S. aureus ATCC 29213			*E. coli* ATCC 25922		
Compound	pH 5	pH 6	pH 7.2	pH 5	pH 6	pH 7.2
Finafloxacin	**0.06**	**0.03**	**0.03**	**0.06**	**0.03**	**0.03**
Ciprofloxacin	2	0.5	0.25	0.5	0.12	0.015
Levofloxacin	1	0.25	0.12	1	0.25	0.03
Gatifloxacin	1	0.25	0.06	1	0.25	0.03
Norfloxacin	8	2	2	2	0.5	0.06

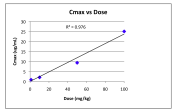
➢ FIN exhibited excellent activity at pH 7.2 against both organisms. Unlike all the other FQs, FIN maintained this activity at lower pH values with MICs of 0.03 µg/mL at pH 6 and 0.06 µg/mL at pH 5.

Panel 3: Pharmacokinetics of Finafloxacin following Subcutaneous Administration in Thigh Infected CD-1 Mice

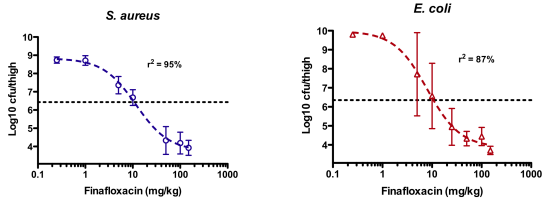


	Finafloxacin Dose - Subcutaneous			
Parameter	1 mg/kg	10 mg/kg	50 mg/kg	100 mg/kg
C_{max} (ug/mL)	0.8	2	9.3	25
AUC $_{0-inf}$ (ug-hr/mL)	0.5	3.6	15.5	43.9
MRT (hr)	0.5	3.6	1.2	1.3
T_{max} (hr)	0.3	0.5	0.5	0.5



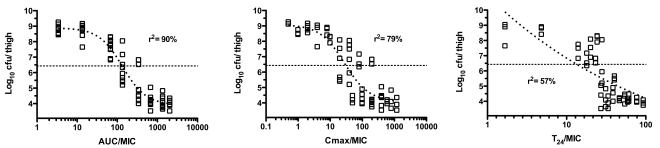


Panel 4: Efficacy of Finafloxacin in the Neutropenic Mouse Thigh Infection Following a Single Dose Administration



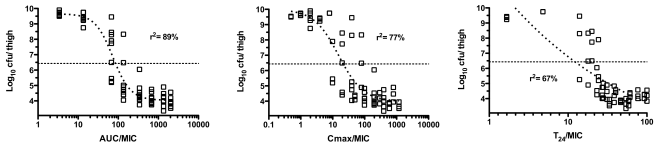
➢ The static dose, no change in CFU counts in treated groups compared to the bacterial burden at the start of treatment, was calculated at 10.7 mg/kg for both the *S. aureus* and *E. coli* infections. Doses corresponding to 1 and 2 log reductions in thigh CFU were 20.4 and 52.5 for *S. aureus* ATCC 29213 and 19.1 and 52.5 mg/kg for *E. coli* ATCC 25922.

Panel 5: PK/PD Parameter Determinations from Dose Fractionation of Finafloxacin Against *Staphylococcus aureus*



➢ For *S. aureus*, the correlations achieved were 90% for AUC/MIC, 79% for C_{max}/MIC and 57% for %$T_{>}$MIC.
➢ The AUC/MIC ratios at stasis, 1 log and 2 log CFU reductions were 132.5, 235.4 and 581.3, respectively.

Panel 6: PK/PD Parameter Determinations from Dose Fractionation of Finafloxacin Against *Escherichia coli*



➢ For *E. coli*, the correlations achieved were 89% for AUC/MIC, 77% for C_{max}/MIC and 67% for %$T_{>}$MIC.
➢ The AUC/MIC ratios at stasis, 1 log and 2 log CFU reductions were 88.1, 134.5 and 312.2, respectively.

Summary and Conclusions

- Finafloxacin was 4- to 16-fold more active than the other fluoroquinolones by MIC testing at pH 5 – pH 6.
- Finafloxacin exhibited a good correlation for the pharmacokinetic parameters of AUC_{0-inf} and C_{max} to dose.
- Finafloxacin exhibited a good correlation between total administered dose and antibacterial effect against both *E. coli* and *S. aureus* in the murine thigh infection model.
- The PK/PD parameter which best predicts finafloxacin activity in this model was AUC/MIC, closely followed by C_{max}/MIC. These parameters are also used to describe the clinical efficacy of marketed fluoroquinolones and could also be utilized to set target exposures in the clinical evaluation of finafloxacin.
- The preliminary PK/PD target of an AUC/MIC of 88.1 for *E. coli* is in the region of those described for other fluoroquinolones to Gram-negative organisms (~125).
- Further testing is warranted with a larger strain set to more accurately define the magnitude of the PK/PD parameter which describe the *in vivo* efficacy of finafloxacin.

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