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Pharmacokinetics (PK) and *In Vivo* Efficacy of Oral Finafloxacin (FIN) and Comparators in Rodent Models of Systemic Infection

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Revised abstract

Background: FIN is a novel fluoroquinolone (FQ) belonging to a new 8-cyano subclass. FIN exhibits optimal efficacy at slightly acidic pH (5.0 - 6.0), under which other FQs show decreased activity. FIN was evaluated in comparison with several best in class FQs; ciprofloxacin (CIP), levofloxacin (LVX) and moxifloxacin (MXF), in *in vivo* bacteraemia models with range of pathogens.

Methods: Serum concentrations were quantified from mice (3 / time point) by bioassay. Bacterial inocula were administered intraperitoneally, treatment commenced 0.5h postinfection and survival monitored over 3 - 5 days. Groups of 5 - 6 female CFW-1 mice or 5 Wistar rats were used. Additionally, treatment of *M. catarrhalis* colonisation was assessed by reduction of bacterial counts ($\Delta \log_{10}$ CFU/mL) in multiple tissues.

Results: The following PK parameters (normalised to 1mg/kg) were determined for **FIN**, MXF, CIP, LVX following oral administration; AUC [kg*h/L] (**0.57**, 0.15, 0.1, 0.22), Cmax [kg/L] (**0.36**, 0.17, 0.04, 0.18), $t_{1/2}$ [h] (**1.52**, 1.26, 1.84, 0.59). The minimum protective oral (or i.v.) doses (i.e. 100% survival) of **FIN** , MXF , CIP, LVX (all mg/kg) in the following bacteraemia models were; *S. aureus* (**10**, 25, 25, >25), MRSA CIP^{RES} (**50**, 50, >50, >50), *E. faecalis* (**1**, >25, >25, 25), VRE (**10**, 10, 25, 25), *S. pneumoniae* (**25**, 25(MXF)), *S. pneumoniae* PEN^{RES} (**25**, 50, >50, 50), *S. pyogenes* (**50**, 50, >50, >50), *E. coli* (**0.5**, 10, 1, 10), *S. marcescens* (i.v., **5**, 5, 0.2, 1), *K. pneumoniae* (**>2.5**, 1, 2.5, 2.5) and *S. pneumoniae* (rat) (**25**, >25, >25, >25). FIN (10mg/kg p.o.) was considerably more active than the other FQs in reducing the viable load of *M. catarrhalis* from the lungs of colonised mice, exhibiting a $\Delta \log_{10}$ CFU/mL of >-3.

Conclusions: FIN, compared with MXF, CIP and LVX exhibited comparative or, in most cases, superior efficacy in rodent bacteraemia models with an extensive range of pathogens.

Introduction

Finafloxacin (FIN, Figure 1) is a novel, broad spectrum fluoroquinolone (FQ) that belongs to a new 8-cyano subclass [1]. FIN contains a novel chiral base component which confers improved antibacterial activity at slightly acidic pH (pH 5.0 – 6.0) under which other marketed FQs exhibit significantly reduced activity [2]. FIN also exhibited superior activity against adherent bacteria *in vitro* [3].

Additionally, FIN displayed an excellent safety profile in a wide range of predictive, *in vitro*, toxicity assays [4] and was well tolerated in healthy human volunteers [5]. These attributes suggest that FIN warrants clinical investigation for bacterial infections that are usually associated with low pH such as urinary tract infection and *Helicobacter pylori* eradication.

FIN displayed favorable pharmacokinetic parameters in mice, when compared alongside several best in class FQs, ciprofloxacin (CIP), levofloxacin (LVX) and moxifloxacin (MXF). The therapeutic potential of FIN was then assessed in a series of rodent bacteremia models.

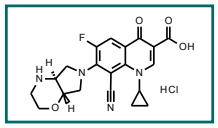


Figure 1. Finafloxacin hydrochloride.

Methods

Pharmacokinetics. Serum concentrations were measured after oral dosing with FIN, MXF, CIP or LVX by bioassay. Blood samples were collected from 3 mice/time point, sera prepared and the concentrations measured by zone diffusion bioassay against *E. coli* or *S. aureus*. AUC, C_{max} and $T_{1/2}$ values were calculated.

Mouse Infections. Overnight cultures of each micro organism were diluted and recultured so that bacteria were in the early logarithmic phase of growth. Female CFW-1 mice, 18 - 20g body weight were infected intraperitoneally (i.p.) with a bacterial suspension in physiological saline or 5% mucin in saline. An inoculum exceeding the LD_{100} was used.

***Enterococcus faecalis* infection** – Groups of 6 mice were infected i.p. with 2.4 x 10^8 CFU/mouse of strain 27159 in 5% mucin. Treatment was by the oral route or by the intravenous (i.v.) route at 30 min post infection with 1, 10, 25 mg/kg of FIN, MXF, CIP, LVX. The survival at 5 days post infection was plotted.

***Moraxella catarrhalis* infection** – Groups of 6 mice were infected i.p. with 1.3 x 10^7 CFU/mouse in 5% mucin. Treatment was by the oral route at 30 min post infection with 1, 10, 25 mg/kg of FIN, MXF, CIP or LVX. On day 1 post infection mice were killed, lungs removed and homogenised (POTTER S Homogeniser) in sterile saline. Viable bacteria were determined by plating serial 10-fold dilutions of the homogenates in duplicate on agar plates. The colony forming units (CFUs) were counted after overnight incubation.

***Escherichia coli* infection** - Groups of 6 mice were infected i.p. with 3.2 x 10^7 CFU /mouse of strain DSM 10650. Treatment was by the oral route at 30 min post infection with 0.1, 0.5, 1.0, or 10 mg/kg of FIN, MXF, CIP or LVX. The survival at 5 days post infection was plotted.

Results and Discussion

Pharmacokinetics (PK)

The PK values are shown in Table 1. FIN had the highest AUC and C_{max} values of the compounds tested. Dose dependency of the C_{max} values after oral administration to mice were almost linear over a dose range of 0 - 225 mg/kg (Figure 2).

Compound	AUC [kg*h/L]	C_{max} [kg/L]	$T_{1/2}$ [Hours]
Finafloxacin	0.571	0.364	1.52
Moxifloxacin	0.153	0.172	1.26
Ciprofloxacin	0.104	0.035	1.84
Levofloxacin	0.223	0.182	0.59

Table 1. Mouse oral PK values (normalised to 1 mg/kg).

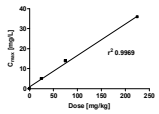


Figure 2. Dose dependency of the C_{max} values after oral administration over a dose range of 0 - 225 mg/kg.

Mouse infection with *Enterococcus faecalis* 27159

FIN was superior to the other FQs when dosed by the oral route with a minimum protective dose of 1 mg/kg in contrast to 25 mg/kg for LVX and >25 mg/kg for MXF and CIP. FIN was also more active when dosed i.v., with 80% protection at 1 mg/kg in contrast to <20% protection with the other three FQs. MXF was as active as FIN *in vitro* (MIC 0.5 mg/L) although being far less active *in vivo* (Figure 3 + 4).

Results and Discussion

Figure 3. Survival at 5 days Post Infection with *E. faecalis* Following Oral Dosing.

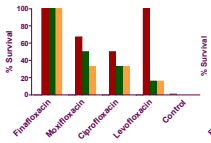
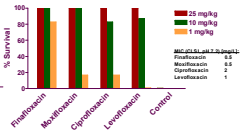


Figure 4. Survival at 5 days Post Infection with *E. faecalis* Following i.v. Dosing.



Mouse Infection with *Escherichia coli* DSM 10650

All compounds showed good activity but FIN was more effective at low doses, with 0.5 mg/kg producing 100% survival and 0.1 mg/kg protecting 60% of infected mice. Although levofloxacin had a low MIC (0.03 mg/L), it was the least active compound *in vivo* (Figure 5).

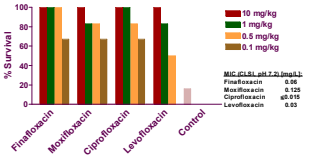


Figure 5. Survival at 5 Days Post Infection with *E. coli* Following Oral Dosing.

Mouse infection with *Moraxella catarrhalis*

FIN showed a greater reduction in the numbers of organisms surviving in the lungs of infected mice at all three dose levels. It was also more active *in vitro* than the three comparator FQs (Figure 6).

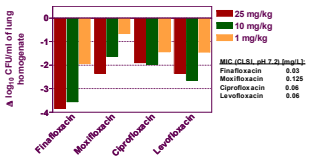


Figure 6. Reduction in CFU of *M. catarrhalis* in lung homogenates.

FIN, MXF, CIP and LVX were evaluated in bacteremia models with an additional and extensive series of pathogens. Efficacy and ranking data are summarised in Table 2.

Table 2. Efficacy of FQs in additional bacteremia models. Minimal protective doses are listed in the order; **FIN**, MXF, CIP, LVX. N; neutropenic.

Infection model	Species	Pathogen	Minimum protective dose (FIN, MXF, CIP, LVX) [mg/kg] Oral	I.V.	Efficacy ranking
Bacteremia	Mouse	*S. aureus*	**10**, 25, 25, >25	**1**, 1, >25, 10	**FIN** ≥ MXF >> LXV > CIP
	Mouse (N)	*S. aureus*		**50**, >50	**FIN** = MXF
	Mouse	*S. aureus* CIP^{RES}	**50**, 50, >50, >50	**50**, 25, >50, >50	MXF ≥ **FIN** >> LVX ≥ CIP
	Mouse (N)	*E. faecalis* (VRE)	**10**, 10, 25, 25		**FIN** = MXF > CIP = LVX
	Mouse	*S. pneumoniae*	**25**, 25	**50**, 50, >50, >50	**FIN** ≥ MXF > LVX = CIP
	Mouse	*S. pneumoniae* PEN^{RES}	**25**, 50, >50, 50		**FIN** ≥ MXF >> LVX ≥ CIP
	Rat	*S. pneumoniae*	**25**, >25, >25, >25		MXF ≥ **FIN** > LVX > CIP
	Mouse	*S. pyogenes*	**50**, 50, >50, >50		**FIN** = MXF >LVX >> CIP
	Mouse (N)	*E. coli*		**1**, 10, 1, 10	**FIN** = CIP > MOX > LEV
	Mouse	*P. aeruginosa*	**>25**, 25	**>25**, 10	CIP >> **FIN**
	Mouse	*S. marcescens*		**5**, 5, 0.2, 1	CIP > LVX ≥ MXF > **FIN**
	Mouse	*K. pneumoniae*	**>2.5**, 1, 2.5, 2.5		MXF ≥ CIP ≥ LVX > **FIN**

Conclusions

- FIN, a new, 8-cyano, broad spectrum FQ has activity *in vivo* against a wide range of pathogenic micro organisms in rodent bacteremia models.
- The results shown here illustrate its superior activity compared with the comparator FQs; MXF, CIP and LVX when administered by the oral route in mouse systemic infections caused by *E. coli* and *E. faecalis*. It was also more active than the other FQs against *M. catarrhalis*, reducing the numbers of organisms in the lungs of infected mice even at low doses.
- These findings, taken together with the good broad spectrum activity *in vitro* against a number of important pathogenic species, including those resistant to other agents, the excellent tolerance seen by the oral route in Phase I studies in man and the lack of toxicity seen in predictive *ex vivo* toxicity tests, indicate that FIN is an excellent candidate for progression to the clinic.

Literature

[1] Wohlert *et al.*, 48th ICAAC, Washington DC 2008, Poster No. F1-2036.
[2] Kresken *et al.*, 48th ICAAC, Washington DC 2008, Poster No. F1-2037.
[3] Goh *et al.*, 48th ICAAC, Washington DC 2008, Poster No. F1-2042.
[4] Schmuck *et al.*, 48th ICAAC, Washington DC 2008, Poster No. F1-2047.
[5] Patel *et al.*, 48th ICAAC, Washington DC 2008, Poster No. F1-2048.