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Efficacy of the investigational fluoroquinolone Finafloxacin in a murine inhalational model of melioidosis

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Introduction

Finafloxacin (Figure 1) is an investigational broad spectrum fluoroquinolone (FQ) belonging to a new 8-cyano subclass [1]. Finafloxacin contains a novel base component which confers improved antibacterial activity at slightly acidic pH conditions (pH 5.0 – 6.0) which would typically reduce the antibacterial activity of other marketed FQ's [2].

Finafloxacin exhibited superior activity to comparator FQ's against slow growing, adherent [3] and intracellular [4] bacteria *in vitro,* including multi-resistant bacteria like MRSA. It also had superior activity in a wide range of rodent infection models [5]. Additionally, finafloxacin displayed an outstanding safety profile in a wide range of *in vitro* assays, *in vivo* animal models and in human phase I-III studies [6] with oral, intraveneous and topical formulations.

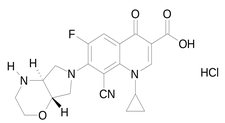


Figure 1 Finafloxacin hydrochloride

Purpose

Finafloxacin is a novel fluoroquinolone in clinical development. It has the unique property of enhanced activity under acidic conditions, unlike other marketed fluoroquinolones. *Burkholderia pseudomallei*, the causative agent of the disease melioidosis, is an intracellular pathogen that can replicate within host organelles where the local pH is acidic. Other fluoroquinolones have reduced antibacterial activity at lower pHs and therefore finafloxacin may offer greater efficacy in the treatment of intracellular infections, especially since it has been shown that finafloxacin is efficiently accumulated within cells in an acidic environment. These studies have been carried out to determine the efficacy of finafloxacin *in vitro* and in a murine model of inhalational melioidosis.

Methods

The efficacy of finafloxacin against two strains of *B. pseudomallei,* K96243 and 576, was investigated. This efficacy was determined *in vitro*, by time kill assays at 4 times the minimal inhibitory concentration (MIC), and *in vivo* against an inhalational challenge of *B. pseudomallei*. Mice were challenged with an average retained dose of approximately 3.8 x 10^2 CFU and treated 6 hours post challenge with 50 mg/kg finafloxacin, ciprofloxacin or 240 mg/kg co-trimoxazole by the oral route. Mice were treated twice a day for 14 days. Groups of mice were culled at 24 hours post-challenge and at cessation of therapy, and livers, lungs and spleens harvested to determine bacterial load. Other groups of animals were monitored for 8 weeks to determine protective efficacy.

Results

MIC testing:

The results showing the antibacterial activity of finafloxacin for two *B. pseudomallei* strains are presented in Table 1. Overall, finafloxacin exhibited the highest *in vitro* activity at acidic conditions (pH 5.0), while ciprofloxacin significantly lost activity under these conditions. Ciprofloxacin and doxycycline were most active at pH 7.0.

Table 1. MICs of selected antibiotics at pH 5 and pH 7 against two *B. pseudomallei* strains.

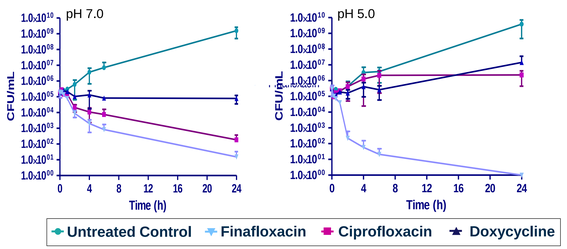
	FINAFLOXACIN		CIPROFLOXACIN		DOXYCYCLINE	
	pH 5	pH 7	pH 5	pH 7	pH 5	pH 7
B. pseudomallei K96243	1	4	32	1	1	0.5
B. pseudomallei 576	2	4	32	1	1	0.5

Time kill assays:

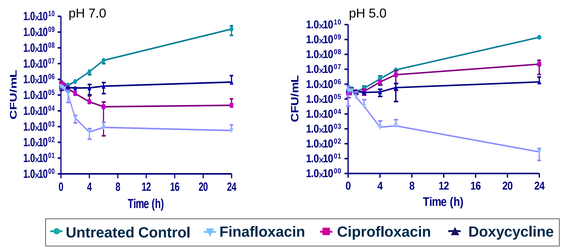
Time kill assays were performed with antibiotics at 4x MIC according to CLSI defined protocols. Results of the experiments are shown in Figure 2. At pH 7.0 finafloxacin exhibits rapid bactericidal activity comparable to or better than ciprofloxacin against both *B. pseudomallei* strains. At pH 5.0 the bactericidal activity of finafloxacin was enhanced whereas ciprofloxacin and doxycycline were bacteriostatic under these conditions.

Figure 2. Time kill assays of finafloxacin with *B. pseudomallei*

***B. pseudomallei* K96243**



***B. pseudomallei* 576**



Murine inhalational infection model with *Burkholderia pseudomallei* K96243

Groups of 10 mice were exposed to aerosolised *B. pseudomallei* K96243 with an average retained dose of 3.76 x 10^2 CFU. The animals were treated orally with 50 mg/kg finafloxacin, 50 mg/kg ciprofloxacin or 240 mg/kg co-trimoxazole twice daily for 14 days. Survival was monitored until day 56. The survival rates are shown in Figure 3. Group of 5 mice per antibiotic were challenged and treated as above and the bacterial load in the spleens, livers and lungs of the animals determined following 1 day and 14 days of therapy. The results are displayed in Figure 4.

Figure 3. Survival data following an inhalational challenge with *B. pseudomallei* K96243

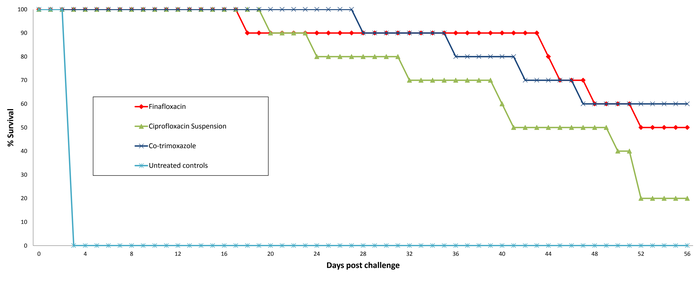
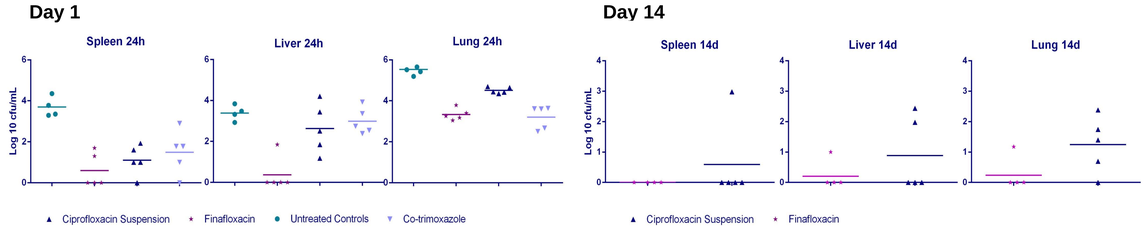


Figure 4. Bacterial loads in organs of mice following inhalational challenge with *B. pseudomallei* K96243



Conclusions

- **At pH 5.0 finafloxacin has superior antimicrobial activity against *B. pseudomallei* compared to ciprofloxacin and doxycycline.**
- **At pH 5.0 and pH 7.0 finafloxacin has faster bactericidal activity against *B. pseudomallei* compared to ciprofloxacin and doxycycline. Ciprofloxacin and doxycycline are bacteriostatic at pH 5.0. No culturable bacteria were detected 24 hours following incubation with finafloxacin at pH 5.0.**
- **Treatment with finafloxacin demonstrated a high level of protection against an inhalational challenge of mice with *B. pseudomallei*. Finafloxacin significantly increased the survival rate of mice exposed to aerosolised *B. pseudomallei* K96243 compared to untreated controls (P<0.05).**
- **Treatment with finafloxacin significantly reduced bacterial load in organs 24 hours after exposure to aerosolised *B. pseudomallei* K96243 compared to untreated controls, ciprofloxacin and co-trimoxazole (P<0.05). After 14 days of therapy 3 out of 5 animals dosed with finafloxacin had cleared the infection from the organs .**
- **These findings suggest that finafloxacin could be an excellent candidate for the treatment of infection with *B. pseudomallei*. Further studies in mice will be conducted to optimise the dose and dosing regimen.**

References

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