The efficacy of finafloxacin against biological threat agents

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Introduction

Burkholderia pseudomallei is the causative agent of melioidosis, a severe and potentially fatal disease. There is currently no vaccine to protect against infection with this organism, therefore effective post-exposure prophylaxis (PEP) are required in the event of a deliberate release. In addition, *B. pseudomallei* is intrinsically resistant to many antimicrobial agents, most apparent in anaerobic acidic conditions that may be encountered *in vivo* and can cause latent infections which are very difficult to treat[1].

Finafloxacin is a novel fluoroquinolone which has demonstrated improved antibacterial activity at acidic pH[2]. Other fluoroquinolones have reduced antibacterial activity at low pH and therefore finafloxacin may offer an advantage in the treatment of intracellular infections, where the local site of infection is acidic[3]. The window of opportunity for finafloxacin against *B. pseudomallei* strain K96243 was compared to co-trimoxazole *in vivo* in a Balb/c mouse model of melioidosis.

Methods

- Balb/c mice were challenged with approximately 98 CFU of *B. pseudomallei* by the inhalational route.
- Treatment was initiated at 24 and 36 hours post-challenge, and continued for 14 days; finafloxacin (37.5 mg/kg) and the vehicle control were administered every 8 hours with co-trimoxazole administered every 12 hours (78 mg/kg), all by the oral route.
- Ten animals per treatment group were left for survival until day 64.
- Culls were performed (n=5 per cull group) following 24 hours and 14 days of treatment. Spleens, livers and lungs were harvested for bacterial load enumeration.

Results

Cull 1 – 24 hours of treatment

- When initiated at 24 h there were less bacteria in all organs harvested from mice treated with finafloxacin compared with those treated with co-trimoxazole ($p<0.01$) (Figure 1A).
- When the homogenates were incubated, two mice treated with finafloxacin were clear in the spleen and liver. All co-trimoxazole treated animals were colonised.
- When initiated at 36 h less bacteria was detected in the livers of mice treated with finafloxacin compared to co-trimoxazole ($p<0.01$) (Figure 1B).
- When the homogenates were incubated, all animals were colonised.

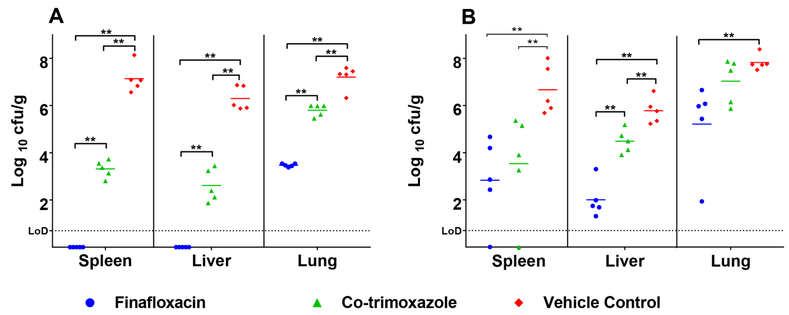

Figure 1. The bacterial load in organs at 24 hours following 24 hours of antibiotic treatment. Bacterial counts (cfu/g) in the spleen, liver and lungs of 5 mice per group following 24 hours of antibiotic treatment initiated at 24 hours (A) or 36 hours (B) post-challenge.

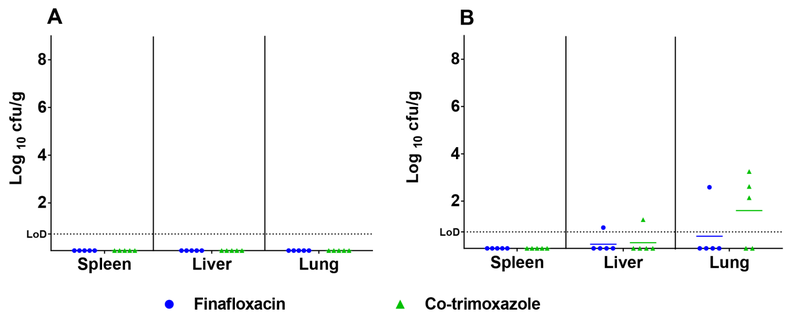

Figure 2. The bacterial load in organs following 14 days of antibiotic treatment. Bacterial counts (cfu/g) in the spleen, liver and lungs of 5 mice per group following 14 days of antibiotic treatment initiated at 24 (A) or 36 (B) hours post-challenge.

Cull 2 – 14 days of treatment

- When initiated at 24 h no bacteria could be detected from the organs harvested from mice treated with finafloxacin or co-trimoxazole (Figure 2A).
- When the homogenates were incubated, all mice treated with finafloxacin were clear. *B. pseudomallei* was recovered from four animals treated with co-trimoxazole.
- When initiated at 36 h two mice treated with finafloxacin were colonised compared to three mice treated with co-trimoxazole (Figure 2B).
- When the homogenates were incubated, three mice treated with finafloxacin were clear compared to one mouse treated with co-trimoxazole.

- Finafloxacin provided 40% protection at day 64 when administered at 24 or 36 hours post-challenge, compared to co-trimoxazole which provided 10%. When the data was combined there was a significant benefit in treating with finafloxacin compared to co-trimoxazole ($p=0.016$).

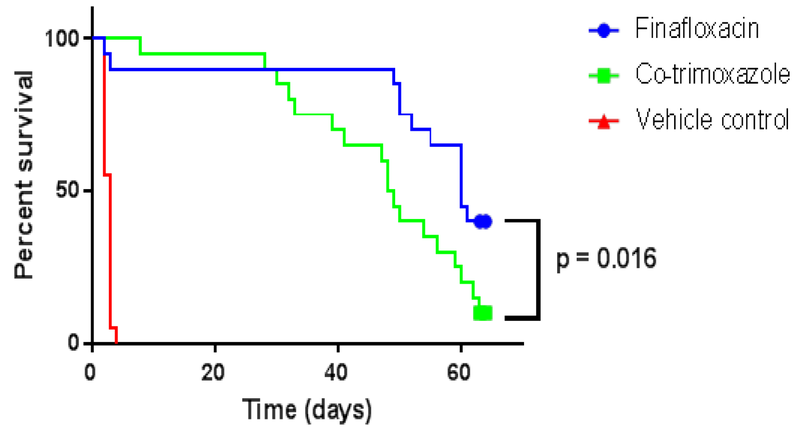

Figure 3. The percentage survival of mice following challenge with *B. pseudomallei*. Mice were challenged with approximately 98 CFU of *B. pseudomallei* by the inhalational route and treated with finafloxacin or the vehicle control every 8 hours or co-trimoxazole every 12 hours by the oral route. Survival data from 24 and 36 hours post-challenge is combined.

Discussion

Treating a *B. pseudomallei* infection with finafloxacin up to 36 hours post-challenge provided an improved level of protection when compared to co-trimoxazole. This is particularly encouraging considering how severely ill these mice were when therapy was initiated. This suggests finafloxacin could be useful for prophylaxis or treatment of infection with *B. pseudomallei* and further investigation of the efficacy is warranted.

References

1. Dance D. Treatment and prophylaxis of melioidosis. *Int J Antimicrob Agents* 2014; 43: 310-318.
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